Harris, A.
09/478977

FILE 'REGISTRY' ENTERED AT 14:19:51 ON 29 AUG 2001
E COLLAGEN TYPE I/CN 5
L1 2 S COLLAGEN TYPE I ?/CN
E COLLAGEN TYPE I/CN

- key terms

FILE 'CAPLUS' ENTERED AT 14:20:43 ON 29 AUG 2001
L1 2 SEA FILE=REGISTRY ABB=ON PLU=ON COLLAGEN TYPE I ?/CN
L2 13324 SEA FILE=CAPLUS ABB=ON PLU=ON L1 OR COLLAGEN(2A)(I OR 1)
L6 4308 SEA FILE=CAPLUS ABB=ON PLU=ON ANGIOGEN?(S)INHIBIT?
L7 64 SEA FILE=CAPLUS ABB=ON PLU=ON L2 AND L6
L8 1 SEA FILE=CAPLUS ABB=ON PLU=ON L7 AND (DENATUR? OR DE NATUR?)
L9 41 SEA FILE=CAPLUS ABB=ON PLU=ON L7 AND (ANTAGONIST? OR MOAB OR MAB OR ANTIBOD? OR HU177 OR HUI77 OR HUI 77 OR HU 177 OR HUIV26 OR HUIV 26 OR XL313 OR XL 313 OR POLYPEPTIDE OR POLYPROTEIN OR PROTEIN OR PEPTIDE OR "NON"(W)PEPTID? OR OLIGO?)
L10 7 SEA FILE=CAPLUS ABB=ON PLU=ON L9 AND ADMIN?
L11 7 SEA FILE=CAPLUS ABB=ON PLU=ON L8 OR L10

L11 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:77331 CAPLUS
DOCUMENT NUMBER: 134:247002
TITLE: Systemic **administration** of a matrix-targeted retroviral vector is efficacious for cancer gene therapy in mice
AUTHOR(S): Gordon, Erlinda M.; Chen, Zhen Hai; Liu, Ling; Whitley, Michelle; Liu, Liqiong; Wei, Denice; Groshen, Susan; Hinton, David R.; Anderson, W. French; Beart, Robert W., Jr.; Hall, Frederick L.
CORPORATE SOURCE: Gene Therapy Laboratories, Division of Colon and Rectal Surgery, Department of Pediatrics, Keck School of Medicine of the University of Southern California, Los Angeles, CA, 90033, USA
SOURCE: Hum. Gene Ther. (2001), 12(2), 193-204
CODEN: HGTHE3; ISSN: 1043-0342
PUBLISHER: Mary Ann Liebert, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Targeting cytocidal vectors to tumors and assocd. vasculature in vivo is a long-standing goal of human gene therapy. In the present study, we demonstrated that i.v. infusion of a matrix (i.e., **collagen**)-targeted retroviral vector provided efficacious gene delivery of a cytocidal mutant cyclin G1 construct (designated MxdnG1) in human cancer xenografts in nude mice. A nontargeted CAE-dnG1 vector (p = 0.014), a control matrix-targeted

vector bearing a marker gene (Mx-nBg; p = 0.004), and PBS served as controls (p = 0.001). Enhanced vector penetration and transduction of tumor nodules (35.7 .+-. 1.4%, mean .+-. SD) correlated with therapeutic efficacy without assocd. toxicity. Kaplan-Meier survival studies were conducted in mice treated with PBS placebo, the nontargeted CAE-dnG1 vector, and the matrix-targeted Mx-dnG1 vector. Using the Tarone log-rank test, the overall p value for comparing all three groups simultaneously was 0.003, with a trend that was significant to a level of 0.004, indicating that the probability of long-term control of tumor growth was significantly greater with the matrix-targeted Mx-dnG1 vector than with the nontargeted CAE-dnG1 vector or PBS placebo. The present study demonstrates that a matrix-targeted retroviral vector deployed by peripheral vein injection (1) accumulated in angiogenic tumor vasculature within 1 h, (2) transduced tumor cells with high-level efficiency, and (3) enhanced therapeutic gene delivery and long-term efficacy without eliciting appreciable toxicity.

REFERENCE COUNT: 34

REFERENCE(S):
(2) Anderson, W; Nature (Suppl) 1998, V392, P25 CAPLUS
(3) Boerger, A; Proc Natl Acad Sci U S A 1999, V96, P9867 CAPLUS
(5) DEPolo, N; J Virol 1999, V73, P6708 CAPLUS
(6) Evans, L; J Virol 1990, V64, P6176 CAPLUS
(7) Fass, D; Science 1997, V277, P1662 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:703597 CAPLUS
DOCUMENT NUMBER: 134:25177

TITLE: Antiangiogenic effect of alpha-anordrin in vitro and in vivo

AUTHOR(S): Ma, Zhong-Cai; Lou, Li-Guang; Zhang, Zhou; Xu, Bin
CORPORATE SOURCE: Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, 200031, Peop. Rep. China

SOURCE: Acta Pharmacol. Sin. (2000), 21(10), 939-944
CODEN: APSCG5
PUBLISHER: Science Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB AIM: To study the antiangiogenic effect of .alpha.-anordrin (.alpha.-Ano), a partial. **antagonist** of estrogen receptor. METHODS: The in vivo **inhibitory** effect of .alpha.-Ano on **angiogenesis** was detd. by microvascular d. (MVD) in tumors and the chicken chorioallantoic membrane (CAM) model. The in vitro effects of .alpha.-Ano on proliferation, migration, and attachment

of human umbilical vein endothelial cells (HUVEC) were assessed by trypan blue exclusion, wound-induced two-dimensional migration model, and their ability to adhere to type I **collagen**, resp. The possible involvement of nitric oxide (NO) in .alpha.-Ano antiangiogenic effect was detd. by measuring NO content using fluorescent assay. RESULTS: .alpha.-Ano significantly **inhibited** the MVD in Lewis lung carcinoma model and this effect was correlated with its **inhibition** of the tumor growth. .alpha.-Ano also showed an **inhibitory** effect on the **angiogenesis** of CAM with the **inhibitory** rate of 53% and such action of .alpha.-Ano could not be blocked by simultaneous **administration** of 17.beta.-estradiol, a typical agonist of estrogen receptor. In vitro studies showed that .alpha.-ANO obviously suppressed the proliferation and migration of HUVEC, but had no obvious effect on the attachment of HUVEC to the type **I collagen**. Moreover, .alpha.-Ano significantly reduced the level of NO released by HUVEC in a dose- and time-dependent manner. CONCLUSION: .alpha.-Ano possesses an antiangiogenic effect, and this effect is mediated, at least in part, by reducing the NO content and subsequently inhibiting the proliferation and migration of endothelial cells.

REFERENCE COUNT: 19

REFERENCE(S):

(1) Brooks, P; Eur J Cancer 1996, V32A, P2423 CAPLUS

(2) Chiarugi, V; Int J Mol Med 1998, V2, P715 CAPLUS

(4) Folkman, J; J Biol Chem 1992, V267, P10931 CAPLUS

(6) Garcia-Cardena, G; J Natl Cancer Inst 1998, V90, P560 CAPLUS

(7) Gu, Z; Acta Physiol Sin 1984, V36, P611 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:475678 CAPLUS

DOCUMENT NUMBER: 133:99569

TITLE: Method and composition for **angiogenesis inhibition** and detection using **antagonists** binding to proteolyzed or **denatured** collagen

INVENTOR(S): Brooks, Peter; Petitclerc, Eric; Xu, Jingsong

PATENT ASSIGNEE(S): University of Southern California, USA

SOURCE: PCT Int. Appl., 92 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000040597	A1	20000713	WO 2000-US383	20000106

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:		
US 1999-114877	P	19990106
US 1999-114878	P	19990106
US 1999-143534	P	19990713
US 1999-152496	P	19990902

AB The invention describes methods for **inhibiting angiogenesis** in a tissue by **administering** an **antagonist** that specifically binds to a proteolyzed or **denatured** collagen but not to native triple helical forms of the collagen. **Antagonists** of the invention can target e.g. **denatured collagens** type **I**, type II, type III, type IV, type V, and combinations thereof. Methods using such **antagonists** for therapeutic treatment of tumor growth, tumor metastasis or of restenosis also are described, as are methods to use such **antagonists** as diagnostic markers of angiogenesis in normal or diseased tissues both in vivo and ex vivo. **Antagonists** include monoclonal **antibodies** referred to as **HUI77**, **HUIV26**, and **XL313**.

REFERENCE COUNT: 3

REFERENCE(S):
(1) Barrach; US 5541295 A 1996 CAPLUS
(2) Bellon, G; Analytical Biochemistry 1985, V150, P188 CAPLUS
(3) Brooks; J Clin Invest 1995, V96, P1815 CAPLUS

L11 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1999:741221 CAPLUS

DOCUMENT NUMBER: 132:103113

TITLE: **Inhibition** by vasoactive intestinal **polypeptide** (VIP) of **angiogenesis** induced by murine Colon 26-L5 carcinoma cells metastasized in liver

AUTHOR(S): Ogasawara, Masaru; Murata, Jun; Kamitani, Yukio; Hayashi, Kazuko; Saiki, Ikuo

CORPORATE SOURCE: Department of Pathogenic Biochemistry, Institute

of Natural Medicine, Toyama Medical and Pharmaceutical University, Toyama, 930-0194, Japan
SOURCE: Clin. Exp. Metastasis (1999), 17(4), 283-291
CODEN: CEXMD2; ISSN: 0262-0898
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We investigated the effect of VIP on the liver metastases and angiogenesis by Colon 26-L5 carcinoma cells in mice. Daily systemic **administration** of VIP, beginning 3 days after tumor inoculation into a portal vein of mice, inhibited significantly the development of their liver metastases. Immunohistochem. staining for factor VIII-related antigen in the sections of liver metastases showed that the systemic **administration** of VIP caused significant prevention of angiogenesis within tumor masses. VIP (10-10 to 10-6 M) inhibited the invasion of reconstituted basement membrane (Matrigel) by hepatic sinusoidal endothelial (HSE) cells in a concn.-dependent manner in a Transwell chamber assay in vitro and achieved approx. 50% redn. of control at 10-6 M. VIP (10-6 M) also significantly suppressed the haptotactic migration of HSE cells to fibronectin, laminin or type **I collagen** substrates with a similar inhibition rate to the invasion assay. Exposure of VIP to HSE cells induced accumulation of intracellular cAMP in a concn.-dependent manner. The inhibitory effect of VIP (10-6 M) on HSE cell migration was significantly abrogated in the presence of 3 .times. 10-6 M H-89, a cAMP-dependent **protein** kinase inhibitor. VIP (10-6 M) inhibited the morphogenesis of HSE cells into capillary-like structures on Matrigel-coated wells. VIP did not affect the proliferation of HSE cells and the prodn. of gelatinases in HSE cells in vitro at the concns. used in the invasion assay. These observations suggest that the anti-metastatic effect of VIP on liver metastases by Colon 26-L5 carcinoma cells in mice is partly due to the prevention of tumor angiogenesis probably through suppression of the motility of endothelial cells.
REFERENCE COUNT: 46
REFERENCE(S):
(1) Ahren, B; Nature 1980, V287, P343 CAPLUS
(2) Arenberg, D; J Exp Med 1996, V184, P981 CAPLUS
(3) Ata, N; Oncol Res 1996, V8, P503 CAPLUS
(4) Barrie, R; J Surg Res 1993, V55, P446 CAPLUS
(5) Cid, M; J Clin Invest 1993, V91, P977 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:691905 CAPLUS
DOCUMENT NUMBER: 131:349791
TITLE: Specific loss of chondromodulin-I gene

expression in chondrosarcoma and the suppression of tumor angiogenesis and growth by its recombinant **protein** in vivo

AUTHOR(S): Hayami, Tadashi; Shukunami, Chisa; Mitsui, Kaori; Endo, Naoto; Tokunaga, Kunihiko; Kondo, Jun; Takahashi, Hideaki E.; Hiraki, Yuji

CORPORATE SOURCE: Department of Orthopaedic Surgery, Niigata University School of Medicine, Niigata, 951-8510, Japan

SOURCE: FEBS Lett. (1999), 458(3), 436-440
CODEN: FEBLAL; ISSN: 0014-5793

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Chondromodulin-I (ChM-I) was previously identified as an **angiogenesis inhibitor** in cartilage. Here, we demonstrated that the level of ChM-I transcripts was substantially reduced to 100 or even less in the lower-grade chondrosarcomas, in articular cartilage or other benign cartilage tumors. We implanted human chondrosarcoma OUMS-27 cells into nude mice that reproducibly produced tumors with cartilaginous matrix. Tumor-induced angiogenesis was evident when the tumors were excised 30 days after implantation. However, the local **administration** of recombinant human ChM-I almost completely blocked vascular invasion and tumor growth in vivo. Moreover, ChM-I also inhibited the growth of HT-29 colon adenocarcinoma in vivo, implying its therapeutic potential for solid tumors.

REFERENCE COUNT: 20

REFERENCE(S):
(1) Bonaventure, J; Exp Cell Res 1994, V212, P97 CAPLUS
(2) Chomczynski, P; Anal Biochem 1987, V162, P156 CAPLUS
(3) Coppola, G; Anticancer Res 1997, V17, P2033 CAPLUS
(4) Gonzalez, A; J Cell Biol 1990, V110, P753 CAPLUS
(5) Hanahan, D; Cell 1996, V86, P353 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1999:620009 CAPLUS

DOCUMENT NUMBER: 132:131881

TITLE: Tubular morphogenesis by genotoxic therapeutic agents that induce NF-.kappa.B activation in human vascular endothelial cells

AUTHOR(S): Goto, Daisuke; Izumi, Hiroto; Ono, Mayumi; Okamoto, Takeshi; Kohno, Kimitoshi; Kuwano, Michihiko

CORPORATE SOURCE: Department of Biochemistry, Kyushu University School of Medicine, Fukuoka, 812-82, Japan
SOURCE: Angiogenesis (1999), Volume Date 1998-1999, 2(4), 345-356
CODEN: AGIOFT; ISSN: 0969-6970
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Angiogenic stimuli induce tubular morphogenesis and angiogenesis in vascular endothelial cells, but these cells are highly vulnerable to cytokines, oxidative stress, and genotoxic anticancer agents. A transcription factor, NF-.kappa.B, is involved in the protection against apoptosis and in angiogenesis in response to stimuli that could induce cell death. NF-.kappa.B was specifically activated by the genotoxic anticancer therapeutic agents etoposide and doxorubicin, but not by bleomycin, mitomycin C and cisplatin, in human vascular endothelial cells in three independent assay systems: nuclear translocation of NF-.kappa.B, binding of NF-.kappa.B to its consensus sequence, and NF-.kappa.B -dependent transcription. Exposure to etoposide and doxorubicin induced tubular morphogenesis by vascular endothelial cells in type **I collagen** gel at rates comparable to tumor necrosis factor-.alpha.. Co-**administration** of NF-.kappa.B antisense **oligonucleotides inhibited** the **angiogenesis** by doxorubicin and etoposide. In contrast, bleomycin, mitomycin C, and cisplatin did not induce angiogenesis. An angiogenic factor, interleukin 8, was dramatically induced in vascular endothelial cells treated with doxorubicin, but not in cells treated with cisplatin. Co-**administration** of anti-interleukin 8 **antibody** almost completely blocked the doxorubicin-induced angiogenesis in vitro, suggesting a paracrine/autocrine control through drug-induced angiogenic factor(s). The presence or absence of NF-.kappa.B activation may have an essential role in tubular morphogenesis by vascular endothelial cells during chemotherapeutic treatment, possibly through interleukin 8.

REFERENCE COUNT: 40
REFERENCE(S):
(1) Abbadie, C; Cell 1993, V75, P899 CAPLUS
(2) Abe, T; J Clin Invest 1993, V92, P54 CAPLUS
(3) Angel, P; Biochim Biophys Acta 1991, V1072, P129 CAPLUS
(4) Baeuerle, P; Annu Rev Immunol 1994, V12, P141 CAPLUS
(5) Baeuerle, P; Biochim Biophys Acta 1991, V1072, P63 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1992:568651 CAPLUS
DOCUMENT NUMBER: 117:168651
TITLE: A model system for tumor angiogenesis: involvement of transforming growth factor-.alpha. in tube formation of human microvascular endothelial cells induced by esophageal cancer cells
AUTHOR(S): Okamura, Kazuki; Morimoto, Akio; Hamanaka, Ryoji; Ono, Mayuni; Kohno, Kimitoshi; Uchida, Yuzo; Kuwano, Michihiko
CORPORATE SOURCE: Dep. Biochem., Oita Med. Univ., Oita, 879-55, Japan
SOURCE: Biochem. Biophys. Res. Commun. (1992), 186(3), 1471-9
CODEN: BBRCA9; ISSN: 0006-291X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Tumor growth is dependent on angiogenesis, which is thought to be mediated through growth factors, such as transforming growth factor-.alpha. (TGF-.alpha.) and -.beta. (TGF-.beta.), epidermal growth factor (EGF), and basic fibroblast growth factor (bFGF), produced by tumor cells. The authors developed a model system for tumor angiogenesis in vitro: tube formation of human omentum microvascular endothelial (HOME) cells in type **I** **collagen** gels when these cells are co-cultured with tumor cells. Exogenously added TGF-.alpha. induced tube formation of HOME cells in collagen gel. In contrast, TGF-.beta. inhibited the TGF-.alpha.-induced tube formation of endothelial cells. The authors investigated whether tube formation could be induced in HOME cells in collagen gel when the HOME cells were co-cultured with three esophageal cancer cell lines, TE1, TE2, and TE5. TE1 and TE2 cells expressed both TGF-.alpha. and TGF-.beta. mRNA, but the level of TGF-.alpha. mRNA in TE2 was much lower than in TE1 cells. TE5 did not express either TGF-.alpha. or TGF-.beta.. The tube formation of HOME cells was induced when they were co-cultured with TE1 cells, while both TE2 and TE5 cell lines induced tube formation at much lower rates than TE1. TE1-induced tube formation of HOME cells was specifically blocked by co-**administration** of anti-TGF-.alpha.-**antibody**, but not by anti-bFGF-**antibody**. Apparently, esophageal tumor angiogenesis is partly controlled by TGF-.alpha., possibly through a paracrine pathway.

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO, CANCERLIT' ENTERED AT 14:28:59 ON 29 AUG 2001)
L12 14 S L8
L13 40 S L10
L14 53 S L12 OR L13

Searcher : Shears 308-4994

L15 21 DUP REM L14 (32 DUPLICATES REMOVED)

L15 ANSWER 1 OF 21 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2001-433094 [47] WPIDS
DOC. NO. CPI: C2001-131053
TITLE: Novel collagen matrix containing transduced subject-derived primary fibroblasts infected with retroviral vector comprising exogenous gene, for implantation in the loose connective tissue of the dermis of a subject.
DERWENT CLASS: B04 D16
INVENTOR(S): ST-LOUIS, D C; VERMA, I M
PATENT ASSIGNEE(S): (SALK) SALK INST BIOLOGICAL STUDIES
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
CA 1341246	C	20010605	(200147)*	EN	50

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
CA 1341246	C	CA 1989-595744	19890405

PRIORITY APPLN. INFO: US 1988-187214 19880428
AN 2001-433094 [47] WPIDS
AB CA 1341246 C UPAB: 20010822
NOVELTY - A **collagen** matrix (I) containing transduced subject-derived primary fibroblasts, for implantation in the loose connective tissue of the dermis of a subject, where the transduced fibroblasts are infected with a recombinant retroviral vector that comprises exogenous genetic material encoding a gene product, where the transduced fibroblasts express the gene product, is new.

ACTIVITY - Antiinfertility.

MECHANISM OF ACTION - Gene therapy. Two artificial tissues containing 4 multiply 106 infected fibroblasts were grafted into the loose connective tissue of the dermis in the midback of a recipient C57BL/6 mouse. To ensure rapid vascularization, a 2-mm2 piece of gelfoam containing 2 mu g of basic fibroblast growth factor was inserted into the loose connective tissue along with each graft. Serum samples were drawn at two day intervals and analyzed for the presence of human factor IX by ELISA. 3 multiply 105-7 multiply 105 of helper-free psi FIXNeo virus were produced in the various cell lines, when assayed by NIH3T3 TK- cells. As measured by ELISA, all

of the virus producing cell lines secreted essentially the same levels of factor IX into the culture media.

USE - (I) is useful in gene therapy in human subjects (claimed), especially useful for the treatment of certain diseases that are caused by gene defects. (I) is useful in fertility control.

ADVANTAGE - Fibroblasts are implanted in a highly vascularized compartment of the skin, and hence they have direct access to the circulatory system. As a result, the needed replacement gene products can easily and efficiently be distributed to other parts of the body. When the gene therapy is no longer needed, the implanted fibroblasts can be conveniently removed. (I) overcomes the inefficient expression of the foreign replacement genes, use of transduced cells that had the potential to be tumorigenic to the animal or individual being treated, use of harsh immunosuppressive agents to avoid the rejection by the animal or individual being treated, necrosis following subcutaneous injection of cells, and poor diffusion of the replacement gene product. Because of the high efficiency of the retroviral proviral infection and expression in fibroblasts, (I) eliminates the need to use marker genes to identify transduced cells. This greatly simplifies the overall problem of introducing replacement genes into cells that will be used for gene therapy. (I) is useful as continuous drug delivery system to replace present regimes that require periodic **administration** of needed substance.

Dwg.0/5

L15 ANSWER 2 OF 21 MEDLINE DUPLICATE 1

ACCESSION NUMBER: 2001344754 MEDLINE
DOCUMENT NUMBER: 21300359 PubMed ID: 11407707
TITLE: Paradoxical effects of tissue inhibitor of metalloproteinases 1 gene transfer in collagen-induced arthritis.
AUTHOR: Apparailly F; Noel D; Millet V; Baker A H; Lisignoli G; Jacquet C; Kaiser M J; Sany J; Jorgensen C
CORPORATE SOURCE: INSERM U475, Montpellier, France.
SOURCE: ARTHRITIS AND RHEUMATISM, (2001 Jun) 44 (6) 1444-54. Journal code: 90M; 0370605. ISSN: 0004-3591.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010709
Last Updated on STN: 20010709
Entered Medline: 20010705

AB OBJECTIVE: The imbalance between matrix metalloproteinases (MMPs) 1, 3, and 9 and their specific **inhibitor**, tissue **inhibitor** of metalloproteinases 1 (TIMP-1), is a critical

step in cartilage injury and **angiogenesis** in arthritis. To explore the therapeutic potential of TIMP-1 gene transfer in erosive arthritis, the effects of an adenoviral vector (Ad-TIMP-1) were assessed in DBA/1 mice with **collagen**-induced arthritis (CIA). METHODS: DBA/1 mice with CIA received an intravenous injection of replication-deficient adenovirus containing the human TIMP-1 gene or a control LacZ gene on day 28 postimmunization. The efficiency of gene transfer was determined by serum TIMP-1 detection, measurements of paw swelling, as well as radiologic and histologic examination of the paws. RESULTS: A single **administration** of Ad-TIMP-1 resulted in detectable serum levels of the exogenous **protein** for at least 13 days. The incidence and onset of arthritis were not statistically modified after human TIMP-1 gene transfer in DBA/1 mice compared with control mice. However, the severity of inflammation was statistically significantly increased in Ad-TIMP-1-treated mice and a similar trend was observed in the histologic and radiologic scores. With regard to the mechanisms of the worsened effect in the Ad-TIMP-1-treated mice, we observed 1) higher serum levels of anti-type II collagen IgG2a, 2) a significant increase in endogenous soluble tumor necrosis factor receptor I (TNFRI) in sera, and 3) increased labeling of mouse tumor necrosis factor alpha and TNFRI within arthritic joints. CONCLUSION: These findings show that overexpression of TIMP-1 does not prevent osteochondral injury in a mouse model of arthritis. Since MMPs have overlapping properties in terms of their roles in extracellular matrix degradation, **angiogenesis**, and shedding of cell surface adhesion molecules, cytokines, and cytokine receptors, the paradoxical results obtained suggest that TIMP-1 is probably not the main **inhibitor** to target.

L15 ANSWER 3 OF 21 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001182503 MEDLINE
DOCUMENT NUMBER: 21097694 PubMed ID: 11166278
TITLE: In vitro tubulogenesis of endothelial cells by relaxation of the coupling extracellular matrix-cytoskeleton.
AUTHOR: Deroanne C F; Lapiere C M; Nusgens B V
CORPORATE SOURCE: Laboratory of Connective Tissues Biology, Tour de Pathologie B23/3, University of Liege, CHU Sart Tilman, B-4000, Liege, Belgium.
SOURCE: CARDIOVASCULAR RESEARCH, (2001 Feb 16) 49 (3) 647-58. Journal code: COR; 0077427. ISSN: 0008-6363.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103

ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010329

AB OBJECTIVE: This investigation aimed at determining the importance of the rigidity of the adhesive support and the participation of the cytoskeleton in tubulogenesis of endothelial cells in vitro. METHODS: The morphotype, biosynthetic phenotype and cytoskeleton organization of human umbilical vein endothelial cells (HUVEC) were analyzed on supports of variable mechanical resistance. RESULTS: Western blot analysis revealed a strong reduction of the expression of actin and focal-adhesion plaque (FAP) proteins in HUVEC organized in tube-like structures (TLS) on soft matrigel or on matrigel co-polymerized with heat-**denatured** collagen as compared to HUVEC remaining in a monolayer pattern on rigid matrigel-coat or on matrigel co-polymerized with type **I collagen**. Human skin fibroblasts morphotype was not altered in these culture conditions and the pattern of FAP proteins and actin was not modulated. By using polyacrylamide gels polymerized with various concentrations of bis-acrylamide to modulate the mechanical resistance of the support and cross-linked to a constant amount of gelatin to provide an equal density of attachment sites, it was shown that the less rigid the support, the more endothelial cells switched to a tube-like pattern. **Collagen** type **I** -induced tubulogenesis was accompanied by a profound and reversible remodeling of the actin-FAP complex suggesting a weakening of the bridging between extracellular matrix (ECM) and the cytoskeleton. Human skin fibroblasts and smooth muscle cells, used as control cells, adhered strongly to the collagen, did not form TLS and their network of actin stress fibers was not remodeled. The **inhibition** of **collagen** type I-induced tubulogenesis by agents altering the actin cytoskeleton-FAP complex including calpain type I **inhibitor**, orthovanadate, KT5720 and jasplakinolide, further supports the determinant role of mechanical coupling between the cells and the matrix in tubulogenesis. CONCLUSIONS: A reduced tension between the endothelial cells and the extracellular matrix, originating in the support or within the cells is sufficient to trigger an intracellular signaling cascade leading to tubulogenesis, an event mimicking one of the last steps of **angiogenesis**.

L15 ANSWER 4 OF 21 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2000-505910 [45] WPIDS
DOC. NO. CPI: C2000-151862
TITLE: Treating brain tumors by **administering peptide** and **antibody antagonists** of the integrins alphav, alphavbeta3 or alphavbeta5.
DERWENT CLASS: B04 D16

INVENTOR(S): LAUG, W E
PATENT ASSIGNEE(S): (CHIL-N) CHILDRENS HOSPITAL LOS ANGELES
COUNTRY COUNT: 86
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000044404	A2	20000803	(200045)*	EN	62

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZA ZW

AU 2000027379 A 20000818 (200057)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000044404	A2	WO 2000-US1949	20000126
AU 2000027379	A	AU 2000-27379	20000126

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000027379 A	Based on	WO 200044404

PRIORITY APPLN. INFO: US 2000-489391 20000121; US 1999-118126 19990201

AN 2000-505910 [45] WPIDS

AB WO 200044404 A UPAB: 20000918
NOVELTY - Methods ((I)-(V)) for **inhibiting** tumor growth, **angiogenesis**, extracellular matrix (ECM)-dependent cell adhesion, vitronectin-dependent cell migration and for inducing apoptosis in brain tumor cells, comprising **administering antagonists (peptides** and **antibodies)** of the integrins alpha v, alpha v beta 3 or alpha v beta 5 , are new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:
(1) a method (I) of inhibiting tumor growth in the brain of a host, comprising **administering** an **antagonists** of an integrin;
(2) a method (II) for **inhibiting angiogenesis** in a tumor tissue located in the brain of a host comprising **administering** a composition comprising an integrin **antagonist** that **inhibits angiogenesis**;

(3) a method (III) of inhibiting extracellular matrix (ECM)-dependent cell adhesion in brain tumor cells growing in the brain of a host, comprising **administering** an **antagonist** to integrins alpha v beta 3 or alpha v beta 5;

(4) a method (IV) of inhibiting vitronectin-dependent cell migration in brain tumor cells growing in the brain of a host, comprising **administering** an **antagonist** to integrin alpha v beta 3; and

(5) a method (V) of inducing apoptosis in tumor cells growing in the brain of a host, comprising **administering** an **antagonist** of an integrin.

ACTIVITY - Cytostatic.

MECHANISM OF ACTION - The **polypeptides** and **antibodies** antagonize the activity of the integrins alpha v, alpha v beta 3 or alpha v beta 5. They also inhibit vitronectin and tenascin-mediated cell adhesion and migration in tumor cells. They further induce direct brain tumor cell death.

Non tissue culture dishes were incubated for 1 hour at 37 deg. C with vitronectin, tenascin, fibronectin and/or **collagen I** (10 micro g/ml), then washed with phosphate buffered saline (PBS). After the wash 5 multiply 105 tumor cells were plated an incubated for 16 hours at 37 deg. C. The cultures were then washed and an adhesion buffer containing 20 micro g/ml of pentapeptide or control **peptide** were added and incubated for a further 24 hours. The cultures were then washed twice with adhesion buffer and stained with Crystal violet and the optical density at 600 nm (OD600) was determined. The more adherent cells present, the higher the OD600. The tumor cell detached from vitronectin and tenascin, whose adherence was mediated by alpha v integrins, but nit from collagen or fibronectin, which interacted with non alpha v integrins. For example with the control **peptide**, 100% of the tumor cells remained attached to all of the extracellular matrix **proteins**, whereas the active **peptide** reduced adhesion the number of cells adhering to 2% (vitronectin) and 40% (tenascin).

USE - The methods and **antagonists** are used to treat brain tissue tumors.

Dwg.0/9

L15 ANSWER 5 OF 21 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD

ACCESSION NUMBER: 2000-465948 [40] WPIDS

DOC. NO. CPI: C2000-140343

TITLE: New **antagonist** that specifically binds to a **denatured** collagen, but binds to the native triple helical form of collagen with substantially reduced affinity, useful for **inhibiting angiogenesis**.

DERWENT CLASS: B04 C06 D16

INVENTOR(S): BROOKS, P; PETITCLERC, E; XU, J
PATENT ASSIGNEE(S): (UYSC-N) UNIV SOUTHERN CALIFORNIA
COUNTRY COUNT: 89
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000040597	A1	20000713	(200040)*	EN	92
AU 2000026032	A	20000724	(200052)		

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW

W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000040597	A1	WO 2000-US383	20000106
AU 2000026032	A	AU 2000-26032	20000106

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000026032	A Based on	WO 200040597

PRIORITY APPLN. INFO: US 1999-152496 19990902; US 1999-114877 19990106; US 1999-114878 19990106; US 1999-143534 19990713

AN 2000-465948 [40] WPIDS

AB WO 200040597 A UPAB: 20000823

NOVELTY - An **antagonist** (I) that specifically binds to a **denatured** collagen, but binds to the native triple helical form of collagen with substantially reduced affinity, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) detecting angiogenesis in a tissue by contacting (I) with the tissue;

(2) detecting tumors or tumor invasion in a tissue by **administering** (I);

(3) screening for **denatured** collagen **antagonists** comprising:

(a) providing a putative **antagonist**;

(b) measuring the putative **antagonists** first affinity for a **denatured** type I, II, III, IV or V collagen;

(c) measuring the putative **antagonists** second affinity for a native type I, II, III, IV or V collagen, where the native collagen selected is the same type as the **denatured** collagen selected; and

(d) selecting the putative **antagonist** as a **denatured** collagen **antagonist** if the second affinity is substantially less than the first affinity;

(4) screening for **denatured** collagen **antagonists** comprising selecting an **antagonist** for the ability to compete with (I) for binding an epitope in **denatured** collagen; and

(5) a **peptide** comprising a sequence encoding an epitope recognized by (I).

ACTIVITY - Cytostatic.

Systemic **administration** of monoclonal **antibody HUIV26** inhibited melanoma tumor growth by 80 % compared to controls.

MECHANISM OF ACTION - **Angiogenesis inhibitor**

Systemic **administration** of monoclonal **antibody XL313 inhibited angiogenesis** in the chick CAM model by over 95 % compared to controls.

USE - To **inhibit angiogenesis** in tissue, especially inflamed tissue. To **inhibit** tumor growth or metastasis, especially melanoma, carcinoma, sarcoma, fibrosarcoma, glioma or astrocytoma. (I) may also be used to **inhibit** psoriasis, macular degeneration or restenosis (claimed). (I) can also be used to treat retinal tissue, e.g. diabetic retinopathy or neovascular glaucoma.

Dwg.0/33

L15 ANSWER 6 OF 21 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2000305394 EMBASE

TITLE: The activity of soluble VCAM-1 in angiogenesis stimulated by IL-4 and IL-13.

AUTHOR: Fukushi J.-I.; Ono M.; Morikawa W.; Iwamoto Y.; Kuwano M.

CORPORATE SOURCE: Dr. J.-I. Fukushi, Department of Medical Biochemistry, Graduate School of Medical Sciences, Kyushu University, Maidashi 3-1-1, Fukuoka 812-8582, Japan. fukushi@mailserver.med.kyushu-u.ac.jp

SOURCE: Journal of Immunology, (1 Sep 2000) 165/5 (2818-2823).
Refs: 49
ISSN: 0022-1767 CODEN: JOIMA3

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
026 Immunology, Serology and Transplantation
030 Pharmacology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB IL-13 is a multifunctional lymphokine sharing a number of biological properties with IL-4. We previously observed that IL-4 shows **angiogenic** activities in vitro as well as in vivo. In this study we examined the effect of IL-13 on **angiogenesis** in vitro and in vivo and also the underlying mechanisms. Human IL-13 significantly stimulated the formation of tube-like structures in collagen gels by human microvascular endothelial cells and bovine aortic endothelial cells by about 3-fold over the controls in the absence of the cytokines. **Administration** of murine IL-13 led to neovascularization when implanted in the rat cornea. Coadministration of neutralizing **mAb** to the IL-4R **inhibited** both tubular morphogenesis in vitro and activation of STAT6 induced by IL-4 or IL-13. Both IL-4 and IL-13 markedly increased mRNA levels of VCAM-1 in vascular endothelial cells, and the production of the soluble form of VCAM-1 was also stimulated in response to IL-4 or IL-13. **Administration** of anti-VCAM-1 Ab in vitro blocked tubular morphogenesis induced by IL-4 and IL-13. **Angiogenesis** induced in vivo in rat cornea by IL-4 and IL-13 was also **inhibited** by Ab against the rat .alpha.4 integrin subunit. These findings suggest that **angiogenesis** dependent on IL-4 and IL-13 is mainly mediated through a soluble VCAM-1/.alpha.4 integrin pathway.

L15 ANSWER 7 OF 21 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000436627 EMBASE
TITLE: Halofuginone: A potent **inhibitor** of critical steps in **angiogenesis** progression.
AUTHOR: Elkin M.; Miao H.-Q.; Nagler A.; Aingorn E.; Reich R.; Hemo I.; Dou H.-L.; Pines M.; Vlodavsky I.
CORPORATE SOURCE: I. Vlodavsky, Department of Oncology, Hadassah Hospital, POB 12000, Jerusalem 91120, Israel. vlodavsk@cc.huji.ac.il
SOURCE: FASEB Journal, (2000) 14/15 (2477-2485).
Refs: 44
ISSN: 0892-6638 CODEN: FAJOEC
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB We have previously demonstrated that halofuginone, a low molecular

weight quinazolinone alkaloid, is a potent **inhibitor** of **collagen** cd (I) and matrix metalloproteinase 2 (MMP-2) gene expression. Halofuginone also effectively suppresses tumor progression and metastasis in mice. These results together with the well-documented role of extracellular matrix (ECM) components and matrix degrading enzymes in formation of new blood vessels led us to investigate the effect of halofuginone on the anglogenic process. In a variety of experimental system, representing sequential events in the **angiogenic** cascade, halofuginone treatment resulted in profound **inhibitory** effect. Among these are the abrogation of endothelial cell MMP-2 expression and basement membrane invasion, capillary tube formation, and vascular sprouting, as well as deposition of subendothelial ECM. The most conclusive anti-**angiogenic** activity of halofuginone was demonstrated in vivo (mouse corneal micropocket assay) by showing a marked **inhibition** of basic fibroblast growth factor (bFGF) -induced neovascularization in response to systemic **administration** of halofuginone, either i.p. or in the diet. The ability of halofuginone to interfere with key events in neovascularization, together with its oral bioavailability and safe use as an anti-parasitic agent, make it a promising drug for further evaluation in the treatment of a wide range of diseases associated with pathological **angiogenesis**.

L15 ANSWER 8 OF 21 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2001455843 IN-PROCESS
DOCUMENT NUMBER: 21393056 PubMed ID: 11501049
TITLE: Antiangiogenic effect of alpha-anordrin in vitro and in vivo.
AUTHOR: Ma Z C; Lou L G; Zhang Z; Xu B
CORPORATE SOURCE: Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 200031, China.
SOURCE: Acta Pharmacol Sin, (2000 Oct) 21 (10) 939-44.
Journal code: DPS; 100956087.
PUB. COUNTRY: China
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20010815
Last Updated on STN: 20010815

AB AIM: To study the antiangiogenic effect of alpha-anordrin (alpha-Ano), a partial **antagonist** of estrogen receptor. METHODS: The in vivo **inhibitory** effect of alpha-Ano on **angiogenesis** was determined by microvascular density (MVD) in tumors and the chicken chorioallantoic membrane (CAM) model. The in vitro effects of alpha-Ano on proliferation, migration, and attachment of human umbilical vein endothelial cells (HUVEC) were assessed by trypan blue exclusion, wound-induced two-dimensional

migration model, and their ability to adhere to type **I collagen**, respectively. The possible involvement of nitric oxide (NO) in alpha-Ano antiangiogenic effect was determined by measuring NO content using fluorescent assay. RESULTS: alpha-Ano significantly **inhibited** the MVD in Lewis lung carcinoma model and this effect was correlated with its **inhibition** of the tumor growth. alpha-Ano also showed an **inhibitory** effect on the **angiogenesis** of CAM with the **inhibitory** rate of 53% and such action of alpha-Ano could not be blocked by simultaneous **administration** of 17 beta-estrodiol, a typical agonist of estrogen receptor. In vitro studies showed that alpha-ANO obviously suppressed the proliferation and migration of HUVEC, but had no obvious effect on the attachment of HUVEC to the type **I collagen**. Moreover, alpha-Ano significantly reduced the level of NO released by HUVEC in a dose- and time-dependent manner. CONCLUSION: alpha-Ano possesses an antiangiogenic effect, and this effect is mediated, at least in part, by reducing the NO content and subsequently **inhibiting** the proliferation and migration of endothelial cells.

L15 ANSWER 9 OF 21 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2001:297550 BIOSIS
DOCUMENT NUMBER: PREV200100297550
TITLE: The anti-**angiogenic** effect of halofuginone (Halo): **Inhibition** of **collagen** type **I** tube formation, matrix metalloproteinase-2 (MMP-2) activities and extracellular matrix (ECM) deposition.
AUTHOR(S): Nagler, A. (1); Elkin, E.; Miao, H.-Q.; Reich, R.; Pines, M.; Vlodavsky, I.
CORPORATE SOURCE: (1) BMT, Hadassah Israel
SOURCE: Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 34a. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology . ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB **Angiogenesis** is essential for the growth and spread of hematooncological tumors. It is a multifactorial process involving type **I collagen** tube formation which directs the migration and assembly of endothelial cells, MMP-2 degradation of ECM **proteins** including collagen and new capillary basement membrane (BM)-like ECM deposition. Halo, a low molecular weight (495Da) quinazolinone alkaloid was previously shown by us to **inhibit collagen** alpha1 (I) gene

expression and synthesis. We therefore hypothesized that Halo may **inhibit angiogenesis**. We evaluated the potential antiangiogenic effect of Halo both in vitro and in vivo using several assays: 1) Capillary-like tube formation with Bovine aortic and human umbilical endothelial cells. 2) Rat aortic ring microvessel formation and 3) Murine micropocket bFGF induced corneal **angiogenesis**. In vitro in the presence of Halo (50 ng/ml) both bovine and human endothelial cells lost their ability to form new capillary vessels and appeared as unorganized cell aggregates. Similarly Halo (100ng/ml) completely **inhibited** microvessel formation from rat aortic rings embedded in **collagen** type **I** gel. As **collagen** type **I** is one of the major constituents of the stroma we evaluated the effect of Halo on ECM deposition by cultured vascular endothelial cells assessed by incorporation of radiolabeled sulfate. Eighty five percent **inhibition** of ECM deposition was observed in cultures incubated with 50ng/ml Halo. In addition microscopic examinations of the denuded culture dishes revealed a very thin or no ECM. We next evaluated the effect of Halo on MMP-2 enzymatic activity by vascular endothelial cells and demonstrated an almost complete **inhibition** of MMP-2 expression and enzymatic activity as well as BM invasion by 100ng/ml Halo. Finally, in vivo Halo **administered** either P.O (5mg/kg) or I.P. (2mg/mouse/day) for 7 days caused profound **inhibition** of bFGF induced corneal neovascularization in the murine micropocket corneal **angiogenesis** model (the area of neovascularization was reduced from 1.7+0.3 mm2 to 0.6+0.2 mm2 in the control and Halo (either P.O or I.P) treated mice, respectively. In summary, Halo **inhibits** several steps in the **angiogenetic** process: MMP-2 expression and BM invasion, capillary-like tube formation and vascular sprouting as well as deposition of subendothelial ECM and finally bFGF induced neovascularization in vivo. This makes Halo a promising candidate for further evaluation in anti-**angiogenic** therapy.

L15 ANSWER 10 OF 21 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 1999391257 MEDLINE
DOCUMENT NUMBER: 99391257 PubMed ID: 10463616
TITLE: **Inhibition** of bladder carcinoma **angiogenesis**, stromal support, and tumor growth by halofuginone.
AUTHOR: Elkin M; Ariel I; Miao H Q; Nagler A; Pines M; de-Groot N; Hochberg A; Vlodavsky I
CORPORATE SOURCE: Department of Oncology, Hadassah-Hebrew University Hospital, Jerusalem, Israel.
CONTRACT NUMBER: CA69646 (NCI)
SOURCE: CANCER RESEARCH, (1999 Aug 15) 59 (16) 4111-8. Journal code: CNF; 2984705R. ISSN: 0008-5472.

Searcher : Shears 308-4994

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 19990925
Last Updated on STN: 19990925
Entered Medline: 19990916

AB We have previously demonstrated that halofuginone, a widely used alkaloid coccidiostat, is a potent inhibitor of **collagen** alpha1(I) and matrix metalloproteinase 2 gene expression. Halofuginone also suppresses extracellular matrix deposition and cell proliferation. We investigated the effect of halofuginone on transplantable and chemically induced mouse bladder carcinoma. In both systems, oral **administration** of halofuginone resulted in a profound anticancerous effect, even when the treatment was initiated at advanced stages of tumor development. Although halofuginone failed to prevent proliferative preneoplastic alterations in the bladder epithelium, it inhibited further progression of the chemically induced tumor into a malignant invasive stage. Histological examination and in situ analysis of the tumor tissue revealed a marked decrease in blood vessel density and in both **collagen** alpha1(I) and H19 gene expression. H19 is regarded as an early marker of bladder carcinoma. The antiangiogenic effect of halofuginone was also demonstrated by inhibition of microvessel formation in vitro. We attribute the profound antitumoral effect of halofuginone to its combined inhibition of the tumor stromal support, vascularization, invasiveness, and cell proliferation.

L15 ANSWER 11 OF 21 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 2000149633 MEDLINE
DOCUMENT NUMBER: 20149633 PubMed ID: 10685372
TITLE: Regeneration of periodontal tissues by basic fibroblast growth factor.
AUTHOR: Murakami S; Takayama S; Ikezawa K; Shimabukuro Y; Kitamura M; Nozaki T; Terashima A; Asano T; Okada H
CORPORATE SOURCE: Department of Periodontology and Endodontology, Osaka University Faculty of Dentistry, Japan.. ipshinya@dent.osaka-u.ac.jp
SOURCE: JOURNAL OF PERIODONTAL RESEARCH, (1999 Oct) 34 (7) 425-30.
Journal code: JMQ; 0055107. ISSN: 0022-3484.
PUB. COUNTRY: Denmark
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Dental Journals; Priority Journals
ENTRY MONTH: 200003

ENTRY DATE: Entered STN: 20000330
Last Updated on STN: 20000330
Entered Medline: 20000323

AB Several growth factors (or cytokines) have recently received attention because of their ability to actively regulate various cellular functions of periodontal ligament (PDL) cells and the effects of topical application of such factor(s) on periodontal tissue regeneration has been evaluated. In this study, we examined the role of basic fibroblast growth factor (bFGF) in the wound healing and regeneration of periodontal tissues. Alveolar bone defects (such as 2-wall, 3-wall and furcation class II bone defects) were created surgically in beagle dogs and primates. Recombinant bFGF was topically applied to the artificial bony defects. Six or 8 wk after application, the periodontal regeneration was morphologically and histomorphometrically analyzed. In all sites where bFGF was applied, significant periodontal ligament formation with new cementum deposits and new bone formation was observed in amounts greater than in the control sites. We found it noteworthy that no instances of epithelial down growth, ankylosis or root resorption were observed in the bFGF sites. In vitro studies demonstrated that bFGF enhances the proliferative responses of human PDL cells, which express FGF receptor-1 and -2, but **inhibits** the induction of alkaline phosphatase activity and mineralized nodule formation by PDL cells. Interestingly, we observed that the mRNA level of laminin in PDL cells, which plays an important role in **angiogenesis**, was specifically upregulated by bFGF stimulation, but that of type **I collagen** was downregulated. The present study demonstrates that bFGF can be applied as one of the therapeutic modalities which actively induce periodontal tissue regeneration. The results of in vitro studies suggest that by suppressing the cytodifferentiation of PDL cells into mineralized tissue forming cells, bFGF may play important roles in wound healing by promoting **angiogenesis** and inducing the growth of immature PDL cells, and may in turn accelerate periodontal regeneration.

L15 ANSWER 12 OF 21 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 2000419668 MEDLINE
DOCUMENT NUMBER: 20388530 PubMed ID: 10935487
TITLE: Inhibition of neovascularization and tumor growth, and facilitation of wound repair, by halofuginone, an inhibitor of **collagen** type **I** synthesis.
AUTHOR: Abramovitch R; Dafni H; Neeman M; Nagler A; Pines M
CORPORATE SOURCE: Department of Biological Regulation, The Weizmann Institute of Science, Rehovot, Israel.
SOURCE: NEOPLASIA, (1999 Oct) 1 (4) 321-9.
Journal code: DRU; 100886622. ISSN: 1522-8002.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20000915
Last Updated on STN: 20000915
Entered Medline: 20000906

AB Halofuginone, an **inhibitor** of **collagen** alpha1(I) gene expression was used for the treatment of subcutaneously implanted C6 glioma tumors. Halofuginone had no effect on the growth of C6 glioma spheroids in vitro, and these spheroids showed no **collagen** alpha1(I) expression and no collagen synthesis. However, a significant attenuation of tumor growth was observed in vivo, for spheroids implanted in CD-1 nude mice which were treated by oral or intraperitoneal (4 microg every 48 hours) **administration** of halofuginone. In these mice, treatment was associated with a dose-dependent reduction in **collagen** alpha1(I) expression and dose- and time-dependent **inhibition** of **angiogenesis**, as measured by MRI. Moreover, halofuginone treatment was associated with improved re-epithelialization of the chronic wounds that are associated with this experimental model. Oral **administration** of halofuginone was effective also in intervention in tumor growth, and here, too, the treatment was associated with reduced **angiogenic** activity and vessel regression. These results demonstrate the important role of **collagen** type I in tumor **angiogenesis** and tumor growth and implicate its role in chronic wounds. **Inhibition** of the expression of **collagen** type I provides an attractive new target for cancer therapy.

L15 ANSWER 13 OF 21 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 2000011098 MEDLINE
DOCUMENT NUMBER: 20011098 PubMed ID: 10545014
TITLE: **Inhibition** by vasoactive intestinal **polypeptide** (VIP) of **angiogenesis** induced by murine Colon 26-L5 carcinoma cells metastasized in liver.
AUTHOR: Ogasawara M; Murata J; Kamitani Y; Hayashi K; Saiki I
CORPORATE SOURCE: Department of Pathogenic Biochemistry, Institute of Natural Medicine, Toyama Medical and Pharmaceutical University, Japan.
SOURCE: CLINICAL AND EXPERIMENTAL METASTASIS, (1999 Jun) 17 (4) 283-91.
Journal code: DFC; 8409970. ISSN: 0262-0898.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199911
ENTRY DATE: Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991119

AB We investigated the effect of VIP on the liver metastases and **angiogenesis** by Colon 26-L5 carcinoma cells in mice. Daily systemic **administration** of VIP, beginning 3 days after tumor inoculation into a portal vein of mice, **inhibited** significantly the development of their liver metastases. Immunohistochemical staining for factor VIII-related antigen in the sections of liver metastases showed that the systemic **administration** of VIP caused significant prevention of **angiogenesis** within tumor masses. VIP (10-(10) to 10(-6) M) **inhibited** the invasion of reconstituted basement membrane (Matrigel) by hepatic sinusoidal endothelial (HSE) cells in a concentration-dependent manner in a Transwell chamber assay in vitro and achieved approximately 50% reduction of control at 10(-6) M. VIP (10(-6) M) also significantly suppressed the haptotactic migration of HSE cells to fibronectin, laminin or type **I** **collagen** substrates with a similar **inhibition** rate to the invasion assay. Exposure of VIP to HSE cells induced accumulation of intracellular cAMP in a concentration-dependent manner. The **inhibitory** effect of VIP (10(-6) M) on HSE cell migration was significantly abrogated in the presence of 3 x 10(-6) M H-89, a cAMP-dependent **protein** kinase **inhibitor**. VIP (10(-6) M) **inhibited** the morphogenesis of HSE cells into capillary-like structures on Matrigel-coated wells. VIP did not affect the proliferation of HSE cells and the production of gelatinases in HSE cells in vitro at the concentrations used in the invasion assay. These observations suggest that the anti-metastatic effect of VIP on liver metastases by Colon 26-L5 carcinoma cells in mice is partly due to the prevention of tumor **angiogenesis** probably through suppression of the motility of endothelial cells.

L15 ANSWER 14 OF 21 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 1998301564 MEDLINE
DOCUMENT NUMBER: 98301564 PubMed ID: 9636139
TITLE: Defining the domains of type **I** **collagen** involved in heparin- binding and endothelial tube formation.
AUTHOR: Sweeney S M; Guy C A; Fields G B; San Antonio J D
CORPORATE SOURCE: Department of Medicine and the Cardeza Foundation for Hematologic Research, Jefferson Medical College of Thomas Jefferson University, Philadelphia, PA 19107, USA.

CONTRACT NUMBER: AR01929 (NIAMS)
KD44494
R29 HL53590 (NHLBI)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1998 Jun 23) 95 (13) 7275-80.
Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199808
ENTRY DATE: Entered STN: 19980817
Last Updated on STN: 20000303
Entered Medline: 19980806

AB Cell surface heparan sulfate proteoglycan (HSPG) interactions with type **I collagen** may be a ubiquitous cell adhesion mechanism. However, the HSPG binding sites on type **I collagen** are unknown. Previously we mapped heparin binding to the vicinity of the type **I collagen** N terminus by electron microscopy. The present study has identified type **I collagen** sequences used for heparin binding and endothelial cell-collagen interactions. Using affinity coelectrophoresis, we found heparin to bind as follows: to type **I collagen** with high affinity (Kd approximately 150 nM); triple-helical peptides (THPs) including the basic N-terminal sequence alpha1(I)87-92, KGHRGF, with intermediate affinities (Kd approximately 2 microM); and THPs including other collagenous sequences, or single-stranded sequences, negligibly (Kd >> 10 microM). Thus, heparin-type **I collagen** binding likely relies on an N-terminal basic triple-helical domain represented once within each monomer, and at multiple sites within fibrils. We next defined the features of type **I collagen** necessary for **angiogenesis** in a system in which type **I collagen** and heparin rapidly induce endothelial tube formation in vitro. When peptides, **denatured** or monomeric type **I collagen**, or type V collagen was substituted for type **I collagen**, no tubes formed. However, when peptides and type **I collagen** were tested together, only the most heparin-avid THPs **inhibited** tube formation, likely by influencing cell interactions with collagen-heparin complexes. Thus, induction of endothelial tube morphogenesis by type **I collagen** may depend upon its triple-helical and fibrillar conformations and on the N-terminal heparin-binding site identified here.

L15 ANSWER 15 OF 21 CANCERLIT

ACCESSION NUMBER: 1998640520 CANCERLIT
DOCUMENT NUMBER: 98640520
TITLE: Tamoxifen down-regulates CD36 mRNA levels in normal and neoplastic human breast tissues (Meeting abstract).
AUTHOR: Anonymous
CORPORATE SOURCE: Breast Cancer Research Laboratory, Fox Chase Cancer Center, Philadelphia, PA, 19111, USA.
SOURCE: Proc Annu Meet Am Assoc Cancer Res, (1997). Vol. 38, pp. A3520.
ISSN: 0197-016X.
DOCUMENT TYPE: (MEETING ABSTRACTS)
FILE SEGMENT: ICDB
LANGUAGE: English
ENTRY MONTH: 199808

AB Tamoxifen (TAM) exerts a long-term suppressive effect on human breast cancer cell proliferation. In order to determine whether the effects of TAM are mediated by specific gene activation or repression, tumoral and normal breast tissues were analyzed by differential display technique (DD). Tissue samples were obtained before and during TAM treatment, from two women in which the diagnosis of invasive ductal carcinoma had been made by incisional biopsy; TAM treatment was **administered** orally at a dose of 20 mg/day for 30 days, prior to performing a modified radical mastectomy. Both tumor and normal breast tissues were frozen at the time of the initial biopsy and from the mastectomy specimens on the 30th day of treatment for obtaining total RNA for DD analysis. The differential display showed a cDNA 202 bp band called AP5-1, in normal and tumor tissues obtained at the time of the biopsy in both patients, but it was down-regulated after TAM treatment. This fragment has 99% homology with the human CD36, a glycoprotein that acts as a receptor for the extracellular matrix **proteins** thrombospondin-1, **collagen** types **I** and IV and oxidized low density lipoprotein (ox-LDL). Differential expression was confirmed by Northern blot hybridization. Since thrombospondin-1 is involved in hematogenous tumor spread, invasion and **angiogenesis**, these results indicate that the down-regulation of CD36 induced by TAM treatment might represent an alternative or additional mechanism of action of this drug. The fact that CD36 also binds ox-LDL suggest that its down-regulation by TAM might play a role in **inhibition** of arteriosclerosis. The multiple functions affected by the down-regulation of CD36 by TAM warrant the need of additional studies utilizing this technique.

L15 ANSWER 16 OF 21 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 95247403 MEDLINE
DOCUMENT NUMBER: 95247403 PubMed ID: 7537258
TITLE: Effect of tecogalan sodium on angiogenesis in vitro

by choroidal endothelial cells.

AUTHOR: Sakamoto T; Ishibashi T; Kimura H; Yoshikawa H; Spee C; Harris M S; Hinton D R; Ryan S J

CORPORATE SOURCE: Doheny Eye Institute, University of Southern California School of Medicine, Los Angeles 90033, USA.

CONTRACT NUMBER: EY03040 (NEI)
EY01545 (NEI)

SOURCE: INVESTIGATIVE OPHTHALMOLOGY AND VISUAL SCIENCE, (1995 May) 36 (6) 1076-83.
Journal code: GWI; 7703701. ISSN: 0146-0404.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199506

ENTRY DATE: Entered STN: 19950608
Last Updated on STN: 19960129
Entered Medline: 19950601

AB PURPOSE. To examine the possible **inhibitory** effect of tecogalan sodium, derived from bacteria, on three important components of in vitro **angiogenesis** (endothelial proliferation, migration, and tube formation in a collagen gel) using bovine choroidal endothelial cells (CECs). METHODS. The effects of tecogalan sodium (1, 5, 25, 125, and 250 micrograms/ml) on cultured CECs were examined when basic fibroblast growth factor (bFGF, 10 ng/ml), vascular endothelial growth factor (VEGF, 50 ng/ml), a combination of bFGF (10 ng/ml) and VEGF (50 ng/ml) (bFGF/VEGF) and 10% fetal calf serum (FCS) were used as **angiogenic** stimulants. For the proliferation assay, CECs were cultured and the cell numbers counted on days 1, 3, and 5. For migration assay, CECs were seeded in the upper half of a Boyden chamber while an **angiogenic** growth factor was loaded in the lower half. After 6 hours of incubation, cell migration was evaluated by counting the numbers of migrated cells per microscopic field on the lower side of the filter. For the tube-forming assay, CECs were seeded in a type **I collagen** gel, and the length of the tube-like structures (an indicator of **angiogenesis**) formed by CECs per microscopic field was quantified by image analysis. The effect of neutralizing **antibody** for bFGF also was tested in these three assays. RESULTS. All tested **angiogenic** stimulants induced CEC proliferation. The stimulatory effect of bFGF and bFGF/VEGF was reduced by tecogalan sodium (IC50 for bFGF effect, 26.1 micrograms/ml). However, the effect of VEGF and of 10% FCS was not altered by low doses of tecogalan sodium (< 25 micrograms/ml). Chemotaxis of CECs was stimulated by bFGF alone and by bFGF/VEGF, and this effect was **inhibited** by tecogalan sodium (IC50

for bFGF, 3.2 micrograms/ml). Stimulation of chemotaxis by VEGF alone and by 10% FCS was not affected by tecogalan sodium in low doses but was **inhibited** by high doses. Tube formation was stimulated by **administration** of each of the factors. Stimulation of tube formation by bFGF and by bFGF/VEGF was **inhibited** by tecogalan sodium (IC50 for bFGF, 18.2 micrograms/ml). High doses of tecogalan sodium (125 and 250 micrograms/ml) also **inhibited** 10% FCS-induced proliferation, migration, and tube formation. CONCLUSION. bFGF, VEGF, and a combination of bFGF and VEGF stimulated proliferation, migration, and tube formation by CECs in vitro. These stimulatory effects, but especially those of bFGF, were **inhibited** by tecogalan sodium. If tecogalan sodium can be shown to have a similar effect in vivo, it might have the potential for pharmacologic control of subretinal neovascularization.

L15 ANSWER 17 OF 21 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 94275235 MEDLINE
DOCUMENT NUMBER: 94275235 PubMed ID: 8006459
TITLE: Expression of 72-kDa gelatinase (MMP-2), collagenase (MMP-1), and tissue metalloproteinase inhibitor (TIMP) in primary pig skin fibroblast cultures derived from radiation-induced skin fibrosis.
AUTHOR: Lafuma C; El Nabout R A; Crechet F; Hovnanian A; Martin M
CORPORATE SOURCE: Laboratoire de Biologie du Tissu Conjonctif, Faculte de Medecine, Universite Paris XII, Creteil, France.
SOURCE: JOURNAL OF INVESTIGATIVE DERMATOLOGY, (1994 Jun) 102 (6) 945-50.
Journal code: IHZ; 0426720. ISSN: 0022-202X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199407
ENTRY DATE: Entered STN: 19940729
Last Updated on STN: 20000303
Entered Medline: 19940719

AB In addition to producing matrix degradation for normal tissue remodeling and repair, matrix metalloproteinases (MMPs) are also involved in various pathologic processes. MMPs and the tissue **inhibitor** of MMPs (TIMP) were investigated in primary cultures of pig fibroblasts from radiation-induced dermal fibrosis and compared to normal dermal fibroblasts. The free gelatinolytic, collagenolytic, and caseinolytic activities secreted into the culture medium were evaluated against specific 3H **denatured collagen** type I, native helical **collagen** , and casein alpha, respectively. The 72- and 68-kilodalton (kDa)

forms of type IV collagenase were investigated by protease zymography and quantified by semi-automated image analysis. Transcription of the interstitial collagenase (MMP-1) and TIMP genes was studied by Northern hybridization analysis. Results revealed that in fibrotic fibroblasts, the amount of MMP-1 mRNA was greatly reduced to undetectable levels whereas the amount of TIMP mRNA was increased fourfold compared to controls. Functional assays using specific 3H substrates demonstrated an overall decrease in free MMP activities. Concomitantly, catheptic collagenolytic activity decreased in fibrotic fibroblast extracts compared to controls. These results indicate that in addition to accumulating large amounts of collagen, proteoglycans, and fibronectin, pig fibroblasts from radiation-induced dermal fibrosis also promote connective tissue matrix formation by repressing MMP-1 and stimulating TIMP expression at the transcriptional level, and by reducing overall free MMP and catheptic collagenolytic activities at the post-transcriptional level. In contrast, enzymography assays and automated image analysis demonstrated no significant change in the 72-kDa type IV collagenase activity of fibrotic pig skin fibroblasts. This opposite regulation of 72-kDa collagenase type IV to that of MMP-1 seems to indicate that it has a specific role in remodeling the extracellular matrix during wound healing, fibrogenesis, and **angiogenesis**.

L15 ANSWER 18 OF 21 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 95034992 MEDLINE
DOCUMENT NUMBER: 95034992 PubMed ID: 7947924
TITLE: Inhibition of tubular morphogenesis in human microvascular endothelial cells by co-culture with chondrocytes and involvement of transforming growth factor beta: a model for avascularity in human cartilage.
AUTHOR: Tada K; Fukunaga T; Wakabayashi Y; Masumi S; Sato Y; Izumi H; Kohno K; Kuwano M
CORPORATE SOURCE: Department of Orthopedics, Oita Medical University, Japan.
SOURCE: BIOCHIMICA ET BIOPHYSICA ACTA, (1994 Nov 11) 1201 (2) 135-42.
Journal code: A0W; 0217513. ISSN: 0006-3002.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199412
ENTRY DATE: Entered STN: 19950110
Last Updated on STN: 19950110
Entered Medline: 19941222
AB Tube formation in collagen gel was induced in human omental

microvascular endothelial (HOME) cells in the presence of epidermal growth factor (EGF) or transforming growth factor-alpha (TGF-alpha). TGF-alpha enhanced the expression of the tissue type plasminogen activator (t-PA) gene, whereas TGF-beta increased the expression of the PA **inhibitor**-1 (PAI-1) gene and **inhibited** that of the t-PA gene. TGF-beta **inhibited** the tube formation of HOME cells in type **I collagen** gel that was enhanced in response to TGF-alpha. We have recently established an **angiogenesis** model in vitro in which vascular endothelial cells on type **I collagen** gel in an inner chamber are co-cultured with other types of cells in an outer chamber. Here we examined whether the EGF/TGF-alpha-induced tube formation in HOME cells was modulated by human chondrocytes co-culture in the outer chamber. TGF-alpha-dependent tube formation of HOME cells was **inhibited** when human chondrocytes were co-cultured in the outer chamber. This chondrocyte-induced **inhibition** of tube formation was partly abrogated by co-**administration** of anti-TGF-beta **antibody**. These findings suggest that TGF-beta is partly involved in the human chondrocyte-dependent **inhibition** of tube formation by human microvascular endothelial cells. This is the first model system demonstrating that avascularity of human chondrocytes is partly due to TGF-beta family produced from them.

L15 ANSWER 19 OF 21 MEDLINE
ACCESSION NUMBER: 92386497 MEDLINE
DOCUMENT NUMBER: 92386497 PubMed ID: 1381275
TITLE: Acidic fibroblast growth factor-Pseudomonas exotoxin chimeric **protein** elicits antiangiogenic effects on endothelial cells.
AUTHOR: Merwin J R; Lynch M J; Madri J A; Pastan I; Siegall C B
CORPORATE SOURCE: Molecular and Cellular Biology, Bristol-Myers Squibb Pharmaceutical Research Institute, Wallingford, Connecticut.
SOURCE: CANCER RESEARCH, (1992 Sep 15) 52 (18) 4995-5001. Journal code: CNF; 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199210
ENTRY DATE: Entered STN: 19921023
Last Updated on STN: 19960129
Entered Medline: 19921008

AB It has recently been shown that chimeric toxins composed of acidic fibroblast growth factor fused to mutant forms of Pseudomonas exotoxin (aFGF-PE) are cytotoxic to a variety of tumor cell lines

with FGF receptors. Although aFGF-PE might be considered as a possible chemotherapeutic toxin, limited knowledge is available concerning its effect on endothelia. This study investigates whether one of the aFGF-PE fusion **proteins**, aFGF-PE664GluKDEL, can function as an anti-**angiogenic** agent. **Protein** synthesis studies using rat epididymal fat pad microvascular endothelial cells (RFCs) indicated that after 24 h in culture, aFGF-PE had a significant **inhibitory** effect on **protein** synthesis at concentrations greater than 100 ng/ml. In cultures incubated with 1000 ng/ml aFGF-PE, RFC **protein** synthesis was **inhibited** as much as 83%. RFCs were also cultured in a 3-dimensional type **I collagen** gel and incubated with either transforming growth factor beta 1, aFGF-PE, or a combination of both. Transforming growth factor beta 1 elicits in vitro **angiogenesis** in these 3-dimensional cultures which consist of rapid formation of complex tubular structures. Transforming growth factor beta 1-treated RFCs incubated with aFGF-PE were unable to produce this **angiogenic** response, nor were they able to migrate out of the 3-dimensional culture to form a monolayer as shown by controls. Cell viability analyses showed that aFGF-PE produced a dose-dependent toxic effect which ranged from 10 to 90% cell death. Competition assays in which the chimeric toxin was preincubated with **antibodies** to aFGF resulted in an 89% reversal of the **inhibitory** effects of aFGF-PE on endothelial cells. Acidic FGF-PE with a mutation in the ADP ribosylation domain of PE was inactive in both 2-dimensional and 3-dimensional cultures. These data show that aFGF-PE has specific in vitro cytotoxic, antiangiogenic, and antimigratory effects on microvascular endothelia.

L15 ANSWER 20 OF 21 MEDLINE DUPLICATE 12

ACCESSION NUMBER: 92378614 MEDLINE
DOCUMENT NUMBER: 92378614 PubMed ID: 1380804
TITLE: A model system for tumor angiogenesis: involvement of transforming growth factor-alpha in tube formation of human microvascular endothelial cells induced by esophageal cancer cells.
AUTHOR: Okamura K; Morimoto A; Hamanaka R; Ono M; Kohno K; Uchida Y; Kuwano M
CORPORATE SOURCE: Department of Biochemistry, Oita Medical University, Japan.
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1992 Aug 14) 186 (3) 1471-9.
Journal code: 9Y8; 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 199209
ENTRY DATE: Entered STN: 19921009
Last Updated on STN: 19960129
Entered Medline: 19920918

AB Tumor growth is dependent on **angiogenesis**, which is thought to be mediated through growth factors, such as transforming growth factor-alpha (TGF-alpha) and -beta (TGF-beta), epidermal growth factor (EGF), and basic fibroblast growth factor (bFGF), produced by tumor cells. We have developed a model system for tumor **angiogenesis** in vitro: tube formation of human omentum microvascular endothelial (HOME) cells in type I **collagen** gels when these cells are co-cultured with tumor cells. Exogenously added TGF-alpha induced tube formation of HOME cells in collagen gel. In contrast, TGF-beta **inhibited** the TGF-alpha-induced tube formation of endothelial cells. We investigated whether tube formation could be induced in HOME cells in collagen gel when the HOME cells were co-cultured with three esophageal cancer cell lines, TE1, TE2, and TE5. TE1 and TE2 cells expressed both TGF-alpha and TGF-beta mRNA, but the level of TGF-alpha mRNA in TE2 was found to be much lower than in TE1 cells. TE5 did not express either TGF-alpha or TGF-beta. The tube formation of HOME cell was induced when they were co-cultured with TE1 cells, while both TE2 and TE5 cell lines induced tube formation at much lower rates than TE1. TE1-induced tube formation of HOME cells was specifically blocked by co-**administration** of anti-TGF-alpha-**antibody**, but not by anti-bFGF-**antibody**. The present study suggests that, in our model system, esophageal tumor **angiogenesis** is partly controlled by TGF-alpha, possibly through a paracrine pathway.

L15 ANSWER 21 OF 21 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1990-037036 [05] WPIDS
DOC. NO. CPI: C1990-016149
TITLE: Collagen implants - for promoting wound healing and releasing bioactive agents.
DERWENT CLASS: A96 B04 B07 D22
INVENTOR(S): CHU, G H; HENDRICKS, D; KSANDER, G; MCMULLIN, H; MCPHERSONJ, M; OGAWA, Y; PRATT, B; MCPHERSON, J M
PATENT ASSIGNEE(S): (CLGE) COLLAGEN CORP
COUNTRY COUNT: 15
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9000060	A	19900111	(199005)*	EN	42
RW: AT BE CH DE FR GB IT LU NL SE					
W: AU JP					
AU 8939646	A	19900123	(199014)		

US 4950483	A	19900821 (199036)		10
EP 428541	A	19910529 (199122)		
R: AT BE CH DE FR GB IT LI LU NL SE				
US 5024841	A	19910618 (199127)		10
JP 04500954	W	19920220 (199214)		13
US 5110604	A	19920505 (199221)		10
US 5219576	A	19930615 (199325)		10
EP 428541	A4	19920506 (199521)		
EP 428541	B1	19950830 (199539)	EN	20
R: AT BE CH DE FR GB IT LI LU NL SE				
DE 68924069	E	19951005 (199545)		
CA 1339007	C	19970325 (199724)		
JP 2820209	B2	19981105 (199849)		12

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 9000060	A		WO 1989-US2799	19890628
US 4950483	A		US 1988-286303	19881216
EP 428541	A		EP 1989-908119	19890628
US 5024841	A		US 1988-213726	19880630
JP 04500954	W		JP 1989-507652	19890628
US 5110604	A		US 1988-213726	19880630
US 5219576	A	Div ex	US 1988-213726	19880630
		Div ex	US 1990-630299	19901219
			US 1991-801732	19911203
EP 428541	A4		EP 1989-908119	
EP 428541	B1		EP 1989-908119	19890628
			WO 1989-US2799	19890628
DE 68924069	E		DE 1989-624069	19890628
			EP 1989-908119	19890628
			WO 1989-US2799	19890628
CA 1339007	C		CA 1989-604382	19890629
JP 2820209	B2		JP 1989-507652	19890628
			WO 1989-US2799	19890628

FILING DETAILS:

PATENT NO	KIND		PATENT NO
US 5219576	A	Div ex	US 5024841
		Div ex	US 5110604
EP 428541	B1	Based on	WO 9000060
DE 68924069	E	Based on	EP 428541
		Based on	WO 9000060
JP 2820209	B2	Previous Publ.	JP 04500954
		Based on	WO 9000060

Searcher : Shears 308-4994

PRIORITY APPLN. INFO: US 1988-213726 19880630; US 1988-286303 19881216

AN 1990-037036 [05] WPIDS

AB WO 9000060 A UPAB: 19930928

Collagen implants comprise a matrix of non-crosslinked atelopeptide collagen fibrils with a dia. of 50-200 nm. The matrix has a density of 0.01-0.3 g/cc and a thickness of 1-20 mm. and have pores at least 80% of which have a dia. of at least 35 microns.

Pref. the implants may also contain 5-500 mcg/ml. heparin as well as growth factors selected from TGF-beta1, TGF-beta2, PDGF-AA, PDGF-AB, PDGF-BB, EGF, acidic or basic FGF, TGF-alpha, connective-tissue-activating **peptides**, beta-thromboglobulin, insulin-like growth factors, tumour necrosis factors, interleukins, colony-stimulating factors, erythropoietin, nerve growth factor and interferons.

USE - The implants are useful for promoting wound healing by promoting connective tissue deposition, **angiogenesis**, re-epithelialisation and fibroplasia. They are also useful for sustained release of bioactive agents, esp. growth factors for promoting wound healing, **inhibiting** tumour growth, modulating the immune system promoting haematopoiesis or inducing or improving bone growth.

0/3

ABEQ US 4950483 A UPAB: 19930928

Collagen sponge compsn. comprises a matrix of density 0.01-0.3 g per cub. cm., thickness 1-20 mm, and has pores 80% or more of which are 35 microns or more in dia. Matrix comprises (a) fibrillar atelopeptide collagen of 50-200 nms dia. which is not chemically cross-linked; and (b) a synergistic wound-healing amt. of TGF-B and FGF (Transforming Growth Factor and Fibroblast Growth Factor). Pref. compsn. includes 5-500 micro-g. per ml. of heparin.

USE - As implants for wound healing, which can promote tissue deposition, angiogenesis, reepithelialisation, and fibroplasia.

ABEQ US 5024841 A UPAB: 19930928

A collagen implant has a matrix of fibrillar atelopeptide collagen whose fibrils are 50-200 nm in dia. are not chemically crosslinked. The matrix density is 0.01-0.3 g/cm3 it is 1-20mm thick and at least 80% of its pores have a dia. at least 35 micrometers. The implant is pref. in the form of an aq. slurry contg. 5-500 microgram heparin per ml. of slurry. Pref. biological growth factor effective for wound healing, oncostasis, osteogenesis or haematopoietic modulation should be present. The growth factor is selected from TGF-beta 1, TGF-beta 2, PDGF-AA, PDGF-BB, PDGF-AB, EGF, acidic or basic FGF, insulin-like growth factors and nerve growth factors etc.

USE/ADVANTAGE - The implant is biocompatible, biodegradable and non-pyrogenic. Implants can promote connective tissue deposition, angiogenesis, reepthelialisation and fibroplasia. @fib

ABEQ US 5110604 A UPAB: 19930928
Wound healing in a mammal is promoted by applying to the wound, a matrix having a density of 0.01-0.3 g/cm3, a thickness of 1-20mm and having pores at least 80% of which are at least 35 microns in dia. The matrix comprises fibrillar atelopeptide collagen. Fibrils are 50-200 mm in dia. and are not chemically crosslinked. Pref., the matrix also comprises a biological growth factor of TGF-beta-1, TGF-beta2, PDGF-AA, PDGF-AB, PDGF-BB, EGF, acidic FGF, basic FGF, TGF-alpha, connective tissue activating **peptides**, beta-thromboglobulin, insulin growth- or tumour necrosis-factor, interleukins, nerve growth factor or interferons.
USE - Wound healing implants and sustained release depots for **administering** bioactive agents.

ABEQ US 5219576 A UPAB: 19931116
Wound healing in a human subject is promoted, by (a) topically applying a matrix of density 0.01-0.3 g per cub. cm., thickness 1-20 mm and pores of which 80% or more have dia. 35 microns or more; and (b) allowing it to remain in contact for growth factor to promote healing. Matrix comprises (i) fibrillar atelopeptide **collagen** of dia. 50-200 nms which are not chemically crosslinked; and (ii) biological growth factor. (e.g. TGF-beta 1).
USE - A implants to promote connective tissue deposition, angiogenesis, reepithelialisation, and fibroplasia.
Dwg.0/2

ABEQ EP 428541 B UPAB: 19951004
A collagen implant, comprising: a matrix having a density of about 0.01 to about 0.3 g/cm3, a thickness of about 1-20 mm, and having pores at least 80% of which are at least 35 micron in diameter, wherein said matrix comprises fibrillar atelopeptide collagen, wherein said fibrils are about 50-200 nm in diameter, and are not chemically cross-linked.
Dwg.0/3

(FILE 'MEDLINE' ENTERED AT 14:35:00 ON 29 AUG 2001)

L16	49313	SEA	FILE=MEDLINE	ABB=ON PLU=ON	COLLAGEN/CT
L17	587	SEA	FILE=MEDLINE	ABB=ON PLU=ON	"ANGIOGENESIS INHIBITORS "/CT
L18	71	SEA	FILE=MEDLINE	ABB=ON PLU=ON	L16 AND L17
L19	56863	SEA	FILE=MEDLINE	ABB=ON PLU=ON	ANTIBODIES/CT
L20	7929	SEA	FILE=MEDLINE	ABB=ON PLU=ON	OLIGONUCLEOTIDES/CT
L21	68354	SEA	FILE=MEDLINE	ABB=ON PLU=ON	PEPTIDES/CT
L22	107584	SEA	FILE=MEDLINE	ABB=ON PLU=ON	PROTEINS/CT
L23	4	SEA	FILE=MEDLINE	ABB=ON PLU=ON	L18 AND (L19 OR L20 OR L21 OR L22)

L16	49313	SEA	FILE=MEDLINE	ABB=ON PLU=ON	COLLAGEN/CT
L17	587	SEA	FILE=MEDLINE	ABB=ON PLU=ON	"ANGIOGENESIS INHIBITORS

"/CT
L18 71 SEA FILE=MEDLINE ABB=ON PLU=ON L16 AND L17
L24 561449 SEA FILE=MEDLINE ABB=ON PLU=ON "ADMINISTRATION & DOSAGE"/CT
L25 10 SEA FILE=MEDLINE ABB=ON PLU=ON L18 AND L24

L26 14 L23 OR L25

L26 ANSWER 1 OF 14 MEDLINE
AN 2001367966 MEDLINE
TI Anti-angiogenic treatment strategies for malignant brain tumors.
AU Kirsch M; Schackert G; Black P M
SO JOURNAL OF NEURO-ONCOLOGY, (2000 Oct-Nov) 50 (1-2) 149-63. Ref: 156
Journal code: JCP; 8309335. ISSN: 0167-594X.
AB The use of angiogenesis inhibitors may offer novel strategies in brain tumor therapy. In contrast to traditional cancer treatments that attack tumor cells directly, angiogenesis inhibitors target at the formation of tumor-feeding blood vessels that provide continuous supply of nutrients and oxygen. With respect to brain tumor therapy, inhibitors of angiogenesis display unique features that are unknown to conventional chemotherapeutic agents. The most important features are independence of the blood-brain barrier, cell type specificity, and reduced resistance. Malignant brain tumors, especially malignant gliomas, are among the most vascularized tumors known. Despite multimodal therapeutic approaches, the prognosis remains dismal. Thus, angiogenesis inhibitors may be highly effective drugs against these tumors. In a clinical setting, they could be applied in the treatment of multiple tumors or postsurgically as an adjuvant therapy to prevent recurrence. This article provides an overview of current anti-angiogenic treatment strategies with emphasis on substances already in clinical trials or candidate substances for clinical trials. The cellular and molecular basis of these substances is reviewed.

L26 ANSWER 2 OF 14 MEDLINE
AN 2001302401 MEDLINE
TI Combination angiostatin and endostatin gene transfer induces synergistic antiangiogenic activity in vitro and antitumor efficacy in leukemia and solid tumors in mice.
AU Scappaticci F A; Smith R; Pathak A; Schloss D; Lum B; Cao Y; Johnson F; Engleman E G; Nolan G P
SO MOLECULAR THERAPY, (2001 Feb) 3 (2) 186-96.
Journal code: DRT; 100890581. ISSN: 1525-0016.
AB Angiostatin and endostatin are potent endothelial cell growth inhibitors that have been shown to inhibit angiogenesis in vivo and tumor growth in mice. However, tumor shrinkage requires chronic delivery of large doses of these proteins. Here we report

synergistic antitumor activity and survival of animals when these factors are delivered in combination to tumors by retroviral gene transfer. We have demonstrated this efficacy in both murine leukemia and melanoma models. Complete loss of tumorigenicity was seen in 40% of the animals receiving tumors transduced by the combination of angiostatin and endostatin in the leukemia model. The synergy was also demonstrated in vitro on human umbilical vein endothelial cell differentiation and this antiangiogenic activity may suggest a mechanism for the antitumor activity in vivo. These findings imply separate pathways by which angiostatin and endostatin mediate their antiangiogenic effects. Together, these data suggest that a combination of antiangiogenic factors delivered by retroviral gene transfer may produce synergistic antitumor effects in both leukemia and solid tumors, thus avoiding long-term administration of recombinant proteins. The data also suggest that novel combinations of antiangiogenic factors delivered into tumors require further investigation as therapeutic modalities.

L26 ANSWER 3 OF 14 MEDLINE
AN 2001269826 MEDLINE
TI Endostatin "cell factories" shrink rodent brain tumors.
AU Brower V
SO Trends Mol Med, (2001 Mar) 7 (3) 97-8.
Journal code: DZY; 100966035. ISSN: 1471-4914.

L26 ANSWER 4 OF 14 MEDLINE
AN 2001225314 MEDLINE
TI Adenovirus-mediated delivery of antiangiogenic genes as an antitumor approach.
AU Regulier E; Paul S; Marigliano M; Kintz J; Poitevin Y; Ledoux C; Roecklin D; Cauet G; Calenda V; Homann H E
SO CANCER GENE THERAPY, (2001 Jan) 8 (1) 45-54.
Journal code: CE3; 9432230. ISSN: 0929-1903.
AB Based on the observation that the growth of solid tumors is dependent on the formation of new blood vessels, therapeutic strategies aimed at inhibiting angiogenesis have been proposed. A number of proteins with angiostatic activity have been described, but their development as therapeutic agents has been hampered by difficulties in their production and their poor pharmacokinetics. These limitations may be resolved using a gene therapy approach whereby the genes are delivered and expressed in vivo. Here we compared adenoviral delivery of endostatin, proliferin-related protein (PRP), and interferon-inducible protein 10 (IP10) genes. Recombinant adenoviruses carrying the three angiostatic genes express biologically active gene products as determined in vitro in endothelial cell proliferation and migration assays, and in vivo by inhibition of neoangiogenesis in rat chambers. Eradication of established tumors in vivo, in the murine B16F10 melanoma model in

immunocompetent mice, was not achieved by intratumoral injection of the different vectors. However, the combination of intravenous plus intratumoral injections allowed rejection of tumors. Ad-PRP or Ad-IP10 were significantly more efficient than Ad-endostatin, leading to complete tumor rejection and prolonged survival in a high proportion of treated animals. These data support the use of in vivo gene delivery approaches to produce high-circulating and local levels of antiangiogenic agents for the therapy of local and metastatic human tumors.

L26 ANSWER 5 OF 14 MEDLINE
AN 2001194899 MEDLINE
TI Clinical studies of angiogenesis inhibitors: the University of Texas MD Anderson Center Trial of Human Endostatin.
AU Herbst R S; Lee A T; Tran H T; Abbruzzese J L
SO Curr Oncol Rep, (2001 Mar) 3 (2) 131-40.
Journal code: DYP; 100888967. ISSN: 1523-3790.
AB Most solid-tumor malignancies remain incurable. Novel agents that target and counteract biologic mechanisms are now being developed. It is hoped that these drugs will allow for more effective, less toxic cancer treatments and long-term maintenance approaches. One important class of agents functions by an anti-angiogenic mechanism, targeting the blood vessel supply of the tumor and inhibiting tumor growth. Several principles are common to these new agents. First, because many of these agents are growth-inhibiting molecules that work exclusively against the tumor vasculature, single agents will have little effect on tumor size in advanced disease. Second, because these agents are relatively non-toxic, they are unlikely to induce the side effects associated with chemotherapy. Because endothelial cells seldom divide in a human host, anti-angiogenic compounds are expected to produce little toxicity. Third, most of these agents work synergistically with chemotherapy and/or radiotherapy. Ironically, combining these relatively non-toxic agents with chemotherapy often produces the toxicities usually associated with anticancer regimens. Anti-angiogenic agents might ultimately be studied in minimal disease. Clinical studies must demonstrate that these agents affect tumor vasculature, and phase I trials should include built-in surrogate endpoints. This article defines the general principles of anti-angiogenic drug action and explains how these principles have been used to design a phase I trial of human endostatin.

L26 ANSWER 6 OF 14 MEDLINE
AN 2001145391 MEDLINE
TI [A fragment of collagen XVIII inhibits angiogenesis].
Et kollagen XVIII-fragment hemmer angiogenese.
AU Zatterstrom U K; Fukai N; Olsen B R
SO TIDSSKRIFT FOR DEN NORSKE LAEGEFORENING, (2000 Nov 30) 120 (29)

3547-50. Ref: 21
Journal code: VRV; 0413423. ISSN: 0029-2001.

AB BACKGROUND: Malignant tumours may produce substances with both stimulatory and inhibitory effect on angiogenesis. MATERIAL AND METHODS: A protein fragment with angiogenesis-inhibiting potential was recently identified in conditioned media from a murine endothelial tumour cell line. RESULTS: The angiogenesis inhibitor, endostatin, is a 20 kDa C-terminal fragment of collagen XVIII, a proteoglycan/collagen found in vessel walls and basement membranes. The generation of endostatin or endostatin-like collagen XVIII fragments is catalyzed by proteolytic enzymes, including cathepsin L and matrix metalloproteases, that cleave peptide bonds within the protease-sensitive hinge region of the C-terminal domain. INTERPRETATION: The physiological processing of collagen XVIII to endostatin may represent a local control mechanism for the regulation of angiogenesis. The outcome of ongoing clinical trials will determine the role of endostatin as a possible angiogenesis-inhibiting drug in the future.

L26 ANSWER 7 OF 14 MEDLINE
AN 2001134523 MEDLINE
TI Antitumor interaction of short course endostatin and ionizing radiation.
AU Greenberger J S
SO CANCER JOURNAL, (2000 Sep-Oct) 6 (5) 279-81. Ref: 20
Journal code: DUN; 100931981. ISSN: 1528-9117.

L26 ANSWER 8 OF 14 MEDLINE
AN 2001120478 MEDLINE
TI Continuous release of endostatin from microencapsulated engineered cells for tumor therapy.
AU Joki T; Machluf M; Atala A; Zhu J; Seyfried N T; Dunn I F; Abe T; Carroll R S; Black P M
SO NATURE BIOTECHNOLOGY, (2001 Jan) 19 (1) 35-9.
Journal code: CQ3. ISSN: 1087-0156.
AB Research studies suggest that tumor-related angiogenesis contributes to the phenotype of malignant gliomas. We assessed the effect of local delivery of the angiogenesis inhibitor endostatin on human glioma cell line (U-87MG) xenografts. Baby hamster kidney (BHK) cells were stably transfected with a human endostatin (hES) expression vector and were encapsulated in alginate-poly L-lysine (PLL) microcapsules for long-term delivery of hES. The release of biologically active endostatin was confirmed using assays of bovine capillary endothelial (BCE) proliferation and of tube formation. Human endostatin released from the microcapsules brought about a 67.2% inhibition of BCE proliferation. Furthermore, secreted hES was able to inhibit tube formation in KDR/PAE cells (porcine aortic endothelial cells stably transfected with KDR, a tyrosine kinase)

treated with conditioned U-87MG medium. A single local injection of encapsulated endostatin-secreting cells in a nude mouse model resulted in a 72.3% reduction in subcutaneous U87 xenografts' weight 21 days post treatment. This inhibition was achieved by only 150.8 ng/ml human endostatin secreted from 2 x 10(5) encapsulated cells. Encapsulated endostatin-secreting cells are effective for the treatment of human glioblastoma xenografts. Continuous local delivery of endostatin may offer an effective therapeutic approach to the treatment of a variety of tumor types.

L26 ANSWER 9 OF 14 MEDLINE
AN 2001120476 MEDLINE
TI Local endostatin treatment of gliomas administered by microencapsulated producer cells.
AU Read T A; Sorensen D R; Mahesparan R; Enger P O; Timpl R; Olsen B R; Hjelstuen M H; Haraldseth O; Bjerkvig R
SO NATURE BIOTECHNOLOGY, (2001 Jan) 19 (1) 29-34.
Journal code: CQ3. ISSN: 1087-0156.
AB We describe a technique for the treatment of malignant brain tumors based on local delivery of the anti-angiogenic protein endostatin from genetically engineered cells encapsulated in ultrapure sodium alginate. Alginate consists of L-guluronic and D-mannuronic acid, which in the presence of divalent cations forms an extended gel network, in which cells reside and remain immunoisolated, when implanted into the rat brain. Here, we show that endostatin-transfected cells encapsulated in alginate maintain endostatin secretion for at least four months after intracerebral implantation in rats. During the implantation period 70% of the encapsulated cells remained viable, as opposed to 85% in in vitro-cultured capsules. Rats that received transplants of BT4C glioma cells, together with endostatin-producing capsules (0.2 microg/ml per capsule), survived 84% longer than the controls. The endostatin released from the capsules led to an induction of apoptosis, hypoxia, and large necrotic avascular areas within 77% of the treated tumors, whereas all the controls were negative. The encapsulation technique may be used for many different cell lines engineered to potentially interfere with the complex microenvironment in which tumor and normal cells reside. The present work may thus provide the basis for new therapeutic approaches toward brain tumors.

L26 ANSWER 10 OF 14 MEDLINE
AN 2001120472 MEDLINE
TI Cell factories for fighting cancer.
AU Bergers G; Hanahan D
SO NATURE BIOTECHNOLOGY, (2001 Jan) 19 (1) 20-1.
Journal code: CQ3. ISSN: 1087-0156.

L26 ANSWER 11 OF 14 MEDLINE
AN 2001111810 MEDLINE
TI The angiogenesis inhibitor endostatin impairs blood vessel maturation during wound healing.
AU Bloch W; Huggel K; Sasaki T; Grose R; Bugnon P; Addicks K; Timpl R; Werner S
SO FASEB JOURNAL, (2000 Dec) 14 (15) 2373-6.
Journal code: FAS. ISSN: 0892-6638.
AB Endostatin is a cleavage product of collagen XVIII that strongly inhibits tumor angiogenesis. To determine if endostatin affects other angiogenic processes, we generated full-thickness excisional wounds on the back of mice that were systemically treated with recombinant murine endostatin. No macroscopic abnormalities of the wound healing process were observed. Histological analysis revealed normal wound contraction and re-epithelialization, but a slight reduction in granulation tissue formation and reduced matrix deposition at the wound edge. The blood vessel density in the wounds of endostatin-treated mice was not affected. However, ultrastructural analysis demonstrated severe abnormalities in blood vessel maturation. The wound vessels in the endostatin-treated mice were narrowed or closed with an irregular luminal surface, resulting in a severe reduction in the number of functional vessels and extravasation of erythrocytes. Endostatin treatment did not affect the expression level and localization of collagen XVIII mRNA and protein. Furthermore, the angiogenesis regulators vascular endothelial growth factor, angiopoietin-1, and angiopoietin-2 were normally expressed in the wounds of endostatin-treated mice. However, expression of the major wound matrix proteins fibronectin and collagens I and III was significantly reduced. This reduction is likely to explain the reduced density of the wound matrix. Our results demonstrate that endostatin treatment reduces the number of functional blood vessels and the matrix density in the granulation tissue, but does not significantly affect the overall wound healing process.

L26 ANSWER 12 OF 14 MEDLINE
AN 2001027454 MEDLINE
TI Expression of antisense to integrin subunit beta 3 inhibits microvascular endothelial cell capillary tube formation in fibrin.
AU Dallabrida S M; De Sousa M A; Farrell D H
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Oct 13) 275 (41) 32281-8.
Journal code: HIV. ISSN: 0021-9258.
AB alpha(v)beta(3) antagonists are potent angiogenesis inhibitors, and several different classes of inhibitors have been developed, including monoclonal antibodies, synthetic peptides, and small organic molecules. However, each class of inhibitor works by the same principal, by blocking the binding of ligands to alpha(v)beta(3). In an effort to develop an alpha(v)beta(3)

inhibitor that down-regulates the actual level of alpha(v)beta(3), we developed an antisense strategy to inhibit alpha(v)beta(3) expression in vitro. beta(3) antisense expressed in endothelial cells specifically down-regulated alpha(v)beta(3) and inhibited capillary tube formation, with the extent of down-regulation correlating with the extent of tube formation inhibition. This inhibition was matrix-specific, since tube formation was not inhibited in Matrigel. These findings support the notion that alpha(v)beta(3) is required for an essential step of angiogenesis in fibrin, namely capillary tube formation. These results suggest that pseudogenetic inhibition of beta(3) integrins using antisense techniques may ultimately provide a therapeutic means to inhibit angiogenesis in vivo.

L26 ANSWER 13 OF 14 MEDLINE
AN 2000210670 MEDLINE
TI Antiangiogenic gene therapy of cancer utilizing a recombinant adenovirus to elevate systemic endostatin levels in mice.
AU Feldman A L; Restifo N P; Alexander H R; Bartlett D L; Hwu P; Seth P; Libutti S K
SO CANCER RESEARCH, (2000 Mar 15) 60 (6) 1503-6.
Journal code: CNF; 2984705R. ISSN: 0008-5472.
AB Gene therapy represents a possible alternative to the chronic delivery of recombinant antiangiogenic proteins to cancer patients. Inducing normal host tissues to produce high circulating levels of these proteins may be more effective than targeting antiangiogenic genes to tumor tissue specifically. Previously reported gene therapy approaches in mice have achieved peak circulating endostatin levels of 8-33 ng/ml. Here we report plasma endostatin levels of 1770 ng/ml after administration of a recombinant adenovirus. Growth of MC38 adenocarcinoma, which is relatively resistant to adenoviral infection, was inhibited by 40%. These findings encourage gene delivery approaches that use the host as a "factory" to produce high circulating levels of antiangiogenic agents.

L26 ANSWER 14 OF 14 MEDLINE
AN 2000207100 MEDLINE
TI Wielding more power over angiogenesis.
AU Habeck M
SO MOLECULAR MEDICINE TODAY, (2000 Apr) 6 (4) 138-9.
Journal code: CMK; 9508560. ISSN: 1357-4310.

FILE 'CAPLUS, MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO, CANCERLIT' ENTERED AT 14:39:27 ON 29 AUG 2001)
L27 3435 S BROOKS P?/AU
L28 19501 S XU J?/AU
L29 98 S PETITCLERC E?/AU
L30 10 S L27 AND L28 AND L29

- Author(s)

Searcher : Shears 308-4994

L31 34 S L27 AND (L28 OR L29)
L32 10 S L28 AND L29
L33 170 S (L27 OR L28 OR L29) AND ANGIOGEN?
L34 2 S L33 AND L2
L35 34 S L30 OR L31 OR L32 OR L34
L36 14 DUP REM L35 (20 DUPLICATES REMOVED)

L36 ANSWER 1 OF 14 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 1
ACCESSION NUMBER: 2001:216319 CAPLUS
DOCUMENT NUMBER: 134:261411
TITLE: Inhibition of angiogenesis in vivo by plasminogen activator inhibitor-1
AUTHOR(S): Stefansson, Steingrimur; **Petitclerc, Eric**; Wong, Michael K. K.; McMahon, Grainne A.; **Brooks, Peter C.**; Lawrence, Daniel A.
CORPORATE SOURCE: Department of Vascular Biology, J. H. Holland Laboratory, Rockville, MD, 20855, USA
SOURCE: J. Biol. Chem. (2001), 276(11), 8135-8141
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The process of angiogenesis is important in both normal and pathol. physiol. However, the mechanisms whereby factors such as basic fibroblast growth factor promote the formation of new blood vessels are not known. In the present study, the authors demonstrate that exogenously added plasminogen activator inhibitor-1 (PAI-1) at therapeutic concns. is a potent inhibitor of basic fibroblast growth factor-induced angiogenesis in the chicken chorioallantoic membrane. By using specific PAI-1 mutants with either their vitronectin binding or proteinase inhibitor activities ablated, the authors show that the inhibition of angiogenesis appears to occur via two distinct but apparently overlapping pathways. The first is dependent on PAI-1 inhibition of proteinase activity, most likely chicken plasmin, while the second is independent of PAI-1's anti-proteinase activity and instead appears to act through PAI-1 binding to vitronectin. Together, these data suggest that PAI-1 may be an important factor regulating angiogenesis in vivo.
REFERENCE COUNT: 65
REFERENCE(S): (1) Argraves, K; J Biol Chem 1995, V270, P26550 CAPLUS
(2) Bacharach, E; Blood 1998, V92, P939 CAPLUS
(3) Bajou, K; Nat Med 1998, V4, P923 CAPLUS
(4) Berkenpas, M; EMBO J 1995, V14, P2969 CAPLUS
(5) Brooks, P; Cell 1994, V79, P1157 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 2 OF 14 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 2
ACCESSION NUMBER: 2000:475678 CAPLUS
DOCUMENT NUMBER: 133:99569
TITLE: Method and composition for **angiogenesis** inhibition and detection using antagonists binding to proteolyzed or denatured collagen
INVENTOR(S): **Brooks, Peter; Petitclerc, Eric; Xu, Jingsong**
PATENT ASSIGNEE(S): University of Southern California, USA
SOURCE: PCT Int. Appl., 92 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000040597	A1	20000713	WO 2000-US383	20000106

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:
US 1999-114877 P 19990106
US 1999-114878 P 19990106
US 1999-143534 P 19990713
US 1999-152496 P 19990902

AB The invention describes methods for inhibiting **angiogenesis** in a tissue by administering an antagonist that specifically binds to a proteolyzed or denatured collagen but not to native triple helical forms of the collagen. Antagonists of the invention can target e.g. denatured **collagens** type **I**, type II, type III, type IV, type V, and combinations thereof. Methods using such antagonists for therapeutic treatment of tumor growth, tumor metastasis or of restenosis also are described, as are methods to use such antagonists as diagnostic markers of **angiogenesis** in normal or diseased tissues both in vivo and ex vivo. Antagonists include monoclonal antibodies referred to as HUI77, HUIV26, and XL313.

REFERENCE COUNT: 3
REFERENCE(S):
(1) Barrach; US 5541295 A 1996 CAPLUS
(2) Bellon, G; Analytical Biochemistry 1985,

V150, P188 CAPLUS
(3) Brooks; J Clin Invest 1995, V96, P1815 CAPLUS

L36 ANSWER 3 OF 14 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 2000:497595 SCISEARCH
THE GENUINE ARTICLE: 300HF
TITLE: Angiogenic cryptic site of subendothelial collagen IV is exposed in ocular neovascular membranes.
AUTHOR: Spee C (Reprint); Hangai M; Lim J I; **Xu J**; **Brooks P C**; Ryan S J
CORPORATE SOURCE: UNIV SO CALIF, DOHENY EYE INST, DEPT OPHTHALMOL, KECK SCH MED, LOS ANGELES, CA; UNIV SO CALIF, KECK SCH MED, NORRIS CANC CTR, DEPT BIOCHEM & MOL BIOL, LOS ANGELES, CA
COUNTRY OF AUTHOR: USA
SOURCE: INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE, (15 MAR 2000) Vol. 41, No. 4, Supp. [S], pp. 41388-41388

Publisher: ASSOC RESEARCH VISION OPHTHALMOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998.
ISSN: 0146-0404.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 0

L36 ANSWER 4 OF 14 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 3
ACCESSION NUMBER: 2000:208665 CAPLUS
DOCUMENT NUMBER: 133:26565
TITLE: New functions for non-collagenous domains of human collagen type IV. Novel integrin ligands inhibiting angiogenesis and tumor growth in vivo
AUTHOR(S): **Petitclerc, Eric**; Boutaud, Ariel; Prestayko, Archie; **Xu, Jingsong**; Sado, Yoshikazu; Ninomiya, Yoshifumi; Sarras, Michael P., Jr.; Hudson, Billy G.; **Brooks, Peter C.**
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, University of Southern California School of Medicine, Los Angeles, CA, 90033, USA
SOURCE: J. Biol. Chem. (2000), 275(11), 8051-8061
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Collagen type IV is a major component of the basal lamina of blood

vessels. Six genetically distinct collagen type IV chains have been identified and are distributed in a tissue-specific manner. Here we define a novel function for sol. non-collagenous (NC1) domains of the .alpha.2(IV), .alpha.3(IV), and .alpha.6(IV) chains of human collagen type IV in the regulation of angiogenesis and tumor growth. These NC1 domains were shown to regulate endothelial cell adhesion and migration by distinct .alpha.v and .beta.1 integrin-dependent mechanisms. Systemic administration of recombinant .alpha.2(IV), .alpha.3(IV), and .alpha.6(IV) NC1 domains potently inhibit angiogenesis and tumor growth, whereas .alpha.1(IV), .alpha.4(IV), and .alpha.5(IV) showed little if any effect. These findings suggest that specific NC1 domains of collagen type IV may represent an important new class of angiogenesis inhibitors.

REFERENCE COUNT: 60

REFERENCE(S):
(1) Blood, C; Biochim Biophys Acta 1990, V1032, P89 CAPLUS
(2) Brooks, P; Cell 1994, V79, P1157 CAPLUS
(3) Brooks, P; Cell 1998, V92, P391 CAPLUS
(4) Brooks, P; Eur J Cancer 1996, V32A, P2423 CAPLUS
(5) Brooks, P; J Clin Invest 1995, V96, P1815 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 5 OF 14 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 2000:496557 SCISEARCH
THE GENUINE ARTICLE: 300HF
TITLE: Angiogenic cryptic site of proteolyzed subendothelial type IV collagen as a novel target to treat retinal neovascularization.
AUTHOR: Hangai M (Reprint); Kitaya N; Chan C K; **Xu J** ; Kim J J; Ryan S J; **Brooks P C**
CORPORATE SOURCE: UNIV SO CALIF, KECK SCH MED, DOHENY EYE INST, DEPT OPHTHALMOL, LOS ANGELES, CA; UNIV SO CALIF, KECK SCH MED, NORRIS CANC CTR, DEPT BIOCHEM & MOL BIOL, LOS ANGELES, CA
COUNTRY OF AUTHOR: USA
SOURCE: INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE, (15 MAR 2000) Vol. 41, No. 4, Supp. [S], pp. 3501-3501. Publisher: ASSOC RESEARCH VISION OPHTHALMOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998. ISSN: 0146-0404.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 0

L36 ANSWER 6 OF 14 BIOSIS COPYRIGHT 2001 BIOSIS

ACCESSION NUMBER: 2000:274291 BIOSIS
DOCUMENT NUMBER: PREV200000274291
TITLE: Angiogenic cryptic site of subendothelial collagen IV is exposed in ocular neovascular membranes.
AUTHOR(S): Spee, C. (1); Hangai, M. (1); Lim, J. I. (1); **Xu, J.**; **Brooks, P. C.**; Ryan, S. J. (1)
CORPORATE SOURCE: (1) Department of Ophthalmology, Doheny Eye Institute, Keck School of Medicine at the University of Southern California, Los Angeles, CA USA
SOURCE: IOVS, (March 15, 2000) Vol. 41, No. 4, pp. S836. print..
Meeting Info.: Annual Meeting of the Association in Vision and Opthalmology. Fort Lauderlade, Florida, USA April 30-May 05, 2000 Association for Research in Vision and Ophthalmology
.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L36 ANSWER 7 OF 14 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2000:275382 BIOSIS
DOCUMENT NUMBER: PREV200000275382
TITLE: Menstrual cycle hormones modulate angiogenesis in ovarian epithelial tumors.
AUTHOR(S): Chen, C. (1); **Petitclerc, E. (1)**; **Brooks, P. C. (1)**; Dubeau, L. (1)
CORPORATE SOURCE: (1) USC/Norris Comprehensive Cancer Ctr, Los Angeles, CA USA
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2000) No. 41, pp. 729. print..
Meeting Info.: 91st Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA April 01-05, 2000
ISSN: 0197-016X.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L36 ANSWER 8 OF 14 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2000:251197 BIOSIS
DOCUMENT NUMBER: PREV200000251197
TITLE: Angiogenic cryptic site of proteolyzed subendothelial type IV collagen as a novel target to treat retinal neovascularization.
AUTHOR(S): Hangai, M. (1); Kitaya, N. (1); Chan, C. K. (1);

Xu, J.; Kim, J. J.; Ryan, S. J. (1); **Brooks, P. C.**
CORPORATE SOURCE: (1) Department of Ophthalmology, Doheny Eye Institute, Keck School of Medicine at the University of Southern California, Los Angeles, CA USA
SOURCE: IOVS, (March 15, 2000) Vol. 41, No. 4, pp. S641. Meeting Info.: Annual Meeting of the Association in Vision and Opthalmology. Fort Lauderlade, Florida, USA April 30-May 05, 2000 Association for Research in Vision and Ophthalmology
.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L36 ANSWER 9 OF 14 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2000:225039 BIOSIS
DOCUMENT NUMBER: PREV200000225039
TITLE: Proteolytic exposure of a cryptic site within collagen-IV regulates angiogenesis and tumor growth in vivo.
AUTHOR(S): **Xu, Jingsong (1)**; Rodriguez, D. (1); Kim, J. J. (1); **Petitclerc, E. (1)**; Hangai, M. (1); Davis, G. E. (1); **Brooks, P. C. (1)**
CORPORATE SOURCE: (1) Univ of Southern CA, Los Angeles, CA USA
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2000) No. 41, pp. 487.
Meeting Info.: 91st Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA April 01-05, 2000
ISSN: 0197-016X.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L36 ANSWER 10 OF 14 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2000:215726 BIOSIS
DOCUMENT NUMBER: PREV200000215726
TITLE: New functions for NC1 domains of human collagen-IV: Novel integrin ligands inhibiting angiogenesis and tumor growth in vivo.
AUTHOR(S): **Petitclerc, Eric (1)**; Boutaud, A. (1); Prestayko, A. (1); **Xu, J. (1)**; Sado, Y. (1); Ninomiya, Y. (1); Hudson, B. G. (1); **Brooks, P. C. (1)**
CORPORATE SOURCE: (1) U Southern CA, Los Angeles, CA USA
SOURCE: Proceedings of the American Association for Cancer

Research Annual Meeting, (March, 2000) No. 41, pp. 487.
Meeting Info.: 91st Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA April 01-05, 2000
ISSN: 0197-016X.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L36 ANSWER 11 OF 14 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 4

ACCESSION NUMBER: 2000:903352 CAPLUS
DOCUMENT NUMBER: 135:91247

TITLE: Generation of monoclonal antibodies to cryptic collagen sites by using subtractive immunization

AUTHOR(S): **Xu, Jingsong**; Rodriguez, Dorothy; Kim, Jenny J.; **Brooks, Peter C.**
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, Norris Cancer Center, University of Southern California Keck School of Medicine, Los Angeles, CA, 90033, USA

SOURCE: Hybridoma (2000), 19(5), 375-385
CODEN: HYBRDY; ISSN: 0272-457X
PUBLISHER: Mary Ann Liebert, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The extracellular matrix (ECM) plays a fundamental role in the regulation of normal and pathol. processes. The most abundantly expressed component found in the ECM is collagen. Triple helical collagen is known to be highly resistant to proteolytic cleavage except by members of the matrix metalloproteinase (MMP) family of enzymes. To date little is known concerning the biochem. consequences of collagen metab. on human diseases. This is due in part to the lack of specific reagents that can distinguish between proteolyzed and triple helical forms of collagen. Here the authors used the technique of subtractive immunization (SI) to generate 2 unique monoclonal antibodies (MAbs HUIV26 and HUI77) that react with denatured and proteolyzed forms of collagen, but show little if any reaction with triple helical collagen. Importantly, HUIV26 and HUI77 react with cryptic sites within the ECM of human melanoma tumors, demonstrating their utility for immunohistochem. anal. in vivo. Thus, the generation of these novel MAbs not only identifies specific cryptic epitopes within triple helical collagen, but also provides important new reagents for studying the roles of collagen remodeling in normal as well as pathol. processes.

REFERENCE COUNT: 38
REFERENCE(S): (4) Brooks, P; Cell 1996, V85, P683 CAPLUS
(5) Brooks, P; Cell 1998, V92, P391 CAPLUS

(6) Brooks, P; J Cell Biol 1993, V122, P1351 CAPLUS
(7) Brooks, P; J Clin Invest 1995, V96, P1815 CAPLUS
(8) Chambers, A; J Natl Cancer Inst 1997, V89, P1260 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 12 OF 14 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 2001044365 MEDLINE
DOCUMENT NUMBER: 20404341 PubMed ID: 10948540
TITLE: The chimeric human/mouse model of angiogenesis.
AUTHOR: **Petitclerc E**; von Schalscha T; **Brooks P C**
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, University of Southern California School of Medicine, Los Angeles, USA.
CONTRACT NUMBER: 1R29CA74132-01 (NCI)
SOURCE: METHODS IN MOLECULAR BIOLOGY, (2000) 137 213-21. Journal code: BU3. ISSN: 1064-3745.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001204

L36 ANSWER 13 OF 14 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 6
ACCESSION NUMBER: 1999:368553 CAPLUS
DOCUMENT NUMBER: 131:156361
TITLE: Integrin .alpha.v.beta.3 promotes M21 melanoma growth in human skin by regulating tumor cell survival
AUTHOR(S): **Petitclerc, Eric**; Stromblad, Staffan; Von Schalscha, Tami L.; Mitjans, Francesc; Piulats, Jaime; Montgomery, Anthony M. P.; Cheresh, David A.; **Brooks, Peter C.**
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, Norris Cancer Center, University of Southern California School of Medicine, Los Angeles, CA, 90033, USA
SOURCE: Cancer Res. (1999), 59(11), 2724-2730 CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: AACR Subscription Office
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Growth and dissemination of malignant melanoma has a profound impact on our population, and little is known concerning the mechanisms controlling this disease in humans. Evidence is provided that integrin .alpha.v.beta.3 plays a crit. role in M21 melanoma tumor survival within human skin by a mechanism independent of its known role in angiogenesis. Antagonists of .alpha.v.beta.3 blocked melanoma growth by inducing tumor apoptosis. Moreover, M21 melanoma cell interactions with denatured collagen, a known ligand for .alpha.v.beta.3, caused a 5-fold increase in the relative Bcl-2:Bax ratio, an event thought to promote cell survival. Importantly, denatured collagen colocalized with .alpha.v.beta.3-expressing melanoma cells in human tumor biopsies, suggesting that .alpha.v.beta.3 interaction with denatured collagen may play a crit. role in melanoma tumor survival in vivo.

REFERENCE COUNT: 24
REFERENCE(S):
(1) Albelda, S; Cancer Res 1990, V50, P6757 CAPLUS
(2) Brooks, P; Cell V79, P1157 CAPLUS
(3) Brooks, P; Cell 1998, V92, P391 CAPLUS
(4) Brooks, P; J Clin Investig 1995, V96, P1815 CAPLUS
(5) Cheresh, D; J Biol Chem 1987, V262, P17703 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L36 ANSWER 14 OF 14 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1999:192867 BIOSIS
DOCUMENT NUMBER: PREV199900192867
TITLE: HER-2/neu (c-erbB2) receptor tyrosine kinase overexpression alters integrin-mediated cell adhesion.
AUTHOR(S): Park, J. M.; **Petitclerc, E.**; Barron, M.; Park, J. J.; **Brooks, P. C.**; Press, M. F.
CORPORATE SOURCE: Univ. Southern California Sch. Med., Los Angeles, CA 90033 USA
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (March, 1999) Vol. 40, pp. 564.
Meeting Info.: 90th Annual Meeting of the American Association for Cancer Research Philadelphia, Pennsylvania, USA April 10-14, 1999 American Association for Cancer Research
. ISSN: 0197-016X.
DOCUMENT TYPE: Conference
LANGUAGE: English

FILE 'HOME' ENTERED AT 14:42:40 ON 29 AUG 2001